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A Systematic Review and Qualitative analysis

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Abbreviations:

H2 Ras: Histamine-2 receptor antagonists;

PPI: Proton Pump Inhibitors;

GORD: Gastro-Oesophageal Reflux disease;

GOR: Gastro-Oesophageal Reflux;

AEs: adverse events;

SAEs: serious adverse events;

NEC: Necrotising enterocolitis;

RCTs: Randomized controlled trials;

DG: Drug-given;

DF: Drug-free;

MII: multichannel intraluminal impedance monitoring;

pH-GOR: GOR episodes detected only by pH monitoring;

aMII-GOR: acid GOR episode detected by MII;

NaMII-GOR: non-acid GOR episode detected by MII;

RIpH: Reflux Index detected only by pH monitoring;

aMII-GOR-BEI: acid MII-GOR-bolus exposure index;

NaMII-GOR-BEI: non-acid MII-GOR-bolus exposure index.

VLBW infants: very low birth weight infants

Abstract

Background

Gastroesophageal reflux is prevalent in preterm infants. Despite widespread use in clinical practice, there is still much controversy over the efficacy and safety of pharmacological interventions, particularly antacid therapy.

Objective

To systematically review the effects of antacid therapy on preterm infants with symptoms of gastroesophageal reflux, and to assess the safety of these interventions.

Methods

We carried out an electronic search of the Cochrane central register of controlled trials (CENTRAL, The Cochrane Library), MEDLINE (1966 – to present), EMBASE (1980- to present) and CINAHL (1982 –to present) as well as other online sources. Participants were preterm infants (<37 weeks gestation) with gastroesophageal reflux disease who were receiving care on a neonatal unit. We assessed the effects of H2 receptor antagonists, PPIs and alginates against placebo, primarily to see if they reduced the symptoms of reflux.

Results

6 studies were included in this review. Meta-analysis could not be carried out due to a lack of studies assessing the same intervention with the same outcomes. Omeprazole therapy significantly reduced the oesophageal acid exposure percentage time with pH<4 ($p<0.01$) and sodium alginate significantly decreased GOR episodes ($p=0.024$). Metoclopramide and ranitidine showed a significant increase in GORD symptoms versus placebo ($p<0.04$). No significant results were found for the use of esomeprazole or lansoprazole versus placebo.

Conclusions

There is insufficient evidence available to conclude whether antacid therapy is effective or safe when treating GORD in preterm infants. Further research is needed into this topic and caution must be taken when administering antacids to preterm infants.

Systematic review registration number: CRD42017078778

Keywords: systematic review; gastroesophageal reflux disease; oesophageal reflux or oesophageal reflux; antacids; histamine receptor antagonists; proton pump inhibitors; alginate; preterm; infant; low birth weight.

What is known?

- Gastroesophageal reflux is a prominent condition among preterm infants.
- Pharmacological interventions are often used to treat GORD, despite the lack of good quality evidence to support its use.
- Studies have shown a significant positive correlation between the use of H2 RAs and important complications.

What is new?

- There is limited evidence supporting the use of antacids in preterm infants
- Omeprazole reduced gastric and oesophageal pH, but did not alter GORD symptoms. Esomeprazole and Lansoprazole had no significant effect on GORD signs and symptoms.
- Combined use of ranitidine and metoclopramide appears counter-effective, with placebo periods giving less bradycardia episodes versus drug periods.

Background

Gastroesophageal reflux is a prominent condition among preterm infants. Despite this, controversy remains over how it should be treated. Currently, non-pharmacologic therapies are generally the first line of treatment in GORD, with pharmacological interventions reserved for those who do not respond .[1]Antacids containing alginate, Histamine-2 receptor antagonists (H2 RAs) and proton pump inhibitors (PPI) are among the most common interventions used with 60%, 53% and 23% of UK neonatal units using these products respectively. [2]

Studies have also shown a significant correlation between the use of H2RAs and important complications. [3, 4] Guillet et al showed H2-blocker use was associated with an increased incidence of NEC (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.34–2.19; P < .0001).

There continues to be a widespread use of the pharmacology therapies in neonatal units today despite the evidence gaps. This review was carried out to systematically evaluate the evidence of efficacy and safety of antacid treatment for GORD in preterm infants and to highlight potential areas for future research.

Objectives

Primary objective:

To assess the effectiveness of antacid therapy in preterm infants diagnosed with gastroesophageal reflux disease.

Secondary objective:

To assess the safety of antacid therapy in preterm infants diagnosed with gastroesophageal reflux disease.

MATERIAL AND METHODS

We used Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Cochrane Handbook of Systematic Reviews of Interventions approach for conducting and reporting systematic reviews and meta-analyses of randomized controlled trials (RCTs).[5,6] The methodology of this systematic review was published in PROSPERO (www.crd.york.ac.uk/PROSPERO; ref CRD42017078778).

Search methods for identification of studies

MEDLINE/PubMed, Embase, Wiley Online Library, Cochrane Library and Web of Science databases were searched to identify trials of antacid therapy in preterm infants. Databases were screened for publications from the earliest available date until October 15, 2017. No language restrictions were applied. Ethical approval was not required because only published articles were included in this review. A database search of clinicaltrials.gov for ongoing and completed trials was also carried out, using the search terms infant or preterm and reflux or gastroesophageal reflux. Trials reported as abstracts or letters to the editor were included if sufficient data to fulfil the inclusion criteria was presented within the report, or provided by authors. Full search strategy is presented in supplementary Appendix 1.

Eligibility criteria

All relevant randomised trials involving preterm infants (<37 weeks gestation) with GORD (clinical diagnosis and/or 24-hour intraoesophageal PH monitoring, or impedance studies) receiving care on a neonatal unit. Crossover, randomised trials or Quasi-randomised studies, described in some way as to suggest or imply that the study was randomised if the demographic detail of each group was similar were included.

Types of interventions

All available antacid therapies for gastro-oesophageal reflux in neonates were included. Antacid therapy (administered by any method) should have been commenced after the diagnosis of GORD and continued for any duration.

The interventions considered were:

- H2 receptor antagonists versus a placebo or standard care.
- Proton pump inhibitors versus a placebo or standard care.
- Alginates versus a placebo or standard care.

Trials were not limited by dose, frequency or duration of intervention.

Selection of studies

Paired reviewers (ED, CM, BS, JD) independently screened titles, abstracts and then full texts for eligibility, assessed risk of bias, and collected data from included studies. Any disagreement between reviewers was resolved through discussion or adjudication by a third reviewer (BS, JD). In case of duplicate publications, the most recent and updated report of the study was included. When necessary, further information was obtained from study authors.

Risk of bias and quality of evidence assessment

The Cochrane Risk-of-Bias Tool was used to assess the risk of bias. [7] The quality of the evidence of outcomes was rated by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8]

Data extraction

From each eligible study the following information was collected: study characteristics (e.g., author name, year of publication, sample size, patient characteristics, antacid type, duration of intervention, dosage, and at least one clinical outcome.

Primary outcomes

- A reduction in reflux symptoms assessed by a reflux index score or clinical symptoms score.

Secondary outcomes

- Time taken to establish full enteral feeds
- Length of hospital stay
- Necrotising enterocolitis (Bell's stage 2 or greater)
- Suspected or proven sepsis
- Other adverse effects

Results

Description of Studies

A total of 20111 articles were identified by the initial search. 18881articles were excluded as duplicates, meta-analysis or other reasons. Thus, 1230 were potentially eligible after title and abstract screening, and 6 studies met our inclusion criteria. (Figure 1) Records identified through the clinicaltrials.gov database were not included as they were either incomplete or did not fit the selection criteria.

All included studies were double-blind, randomised, placebo-controlled trials. 4 of the 6 were cross-over trials (Wheatley et al[9], Omari et al[10], Corvaglia (a) et al[11], Corvaglia (b) et al[12]), whilst the remaining 2 were parallel trials (Orenstein et al[13], Davidson et al[14]).

The main characteristics of included RCTs are described in Table 1 and excluded studies are summarized in supplementary appendix 2.

Table 1 - Characteristics of Included Studies

Studies	Corvaglia (a) et al[11]	Corvaglia (b) et al[12]	Davidson et al[14]	Omari et al[10]	Orenstein et al[13]	Wheatley et al[9]
Methods	Clinical trial - cross-over of treatment and placebo	Clinical trial - cross-over of treatment and placebo	Randomised, double blind, placebo controlled trial	Randomised, controlled, double-blind trial - crossover design	Randomised Controlled Trial - multicentre, double-blind, parallel-group study	Randomised, controlled, masked cross-over study
Participants	32 Preterm newborns (gestational age ≤33 weeks) with symptoms of GOR (frequent regurgitations and/or postprandial desaturations)	28 Preterm newborns (gestational age ≤33 weeks) with recurrent postprandial apnoeas.	52 Term infants or with a gestational or post-conceptional age of 28 to 44 weeks	10 Preterm infants with a mean postmenstrual age of 36.1 ± 0.7 (range, 34-40 weeks)	162 Infants aged 16 weeks (median, range 4-51) gestation at birth 35 weeks (median, range 25-39)	18 Preterm infants having >3 bradycardia episodes per 2 days
Interventions	0.25 ml/kg sodium alginate was given four times at alternate meals (‘drug-given’ (DG) meals), remaining four meals were placebo (‘drug-free’ (DF) meals)	0.25 ml/kg sodium alginate after one single meal ("drug given" meal) or placebo ("drug free" meal)	Esomeprazole 0.5 mg/kg or placebo	0.7mg/kg omeprazole once daily or placebo	Lansoprazole administered once daily at 0.2 to 0.3 mg/kg/day for infants age ≤10 weeks and at 1.0 to 1.5 mg/kg/day for those age >10 weeks or placebo administered identically but without active drug.	Metoclopramide, 0.2 mg/kg/dose every 6 hours, and ranitidine, 2 mg/kg/dose every 8 hours, with saline placebo.
Outcomes	Gastro-oesophageal reflux features	Apnoea episodes, Gastroesophageal episodes	Vomiting, Neurobehavioural, Back Arching, Gagging, Irritability/crying/fussing, Bradycardia, Oxygen Desaturation, Apnoea	Oesophageal pH, Gastric pH, Vomiting, Apnoea, Bradycardia, Choking, Behavioural changes, Blood biochemistry, Blood picture	Crying, Regurgitation, Stop feeding, Refuse feed, Arching back, Wheezing, Coughing, Hoarseness, Adverse Events	Bradycardia episodes per day.

Risks of Bias assessments of trials are summarized in Figure 2 and supplementary Appendix 3. The evaluations of the level of evidence of outcomes according to the GRADE approach are summarized in supplementary Appendix 4.

A total of 302 participants were enrolled in the 6 included trials, of which, 4 studies included only preterm infants. Omari et al[10] included preterm infants between 34 and 40 weeks gestational age, Corvaglia (a) et al[11] and Corvaglia (b) et al [12] included ≤33 weeks gestational age and Wheatley et al [9] included those with a gestational age of <37 weeks at birth and a corrected gestational age at enrolment of <44 weeks. Orenstein et al[13] and Davidson et al[14] included both preterm infants and full-term infants.

Primary Outcome: All 6 studies assessed various reflux symptoms (See Appendix 5 in supplement). The inclusion criteria for each study defined GORD differently. Omari et al, Corvaglia (a) et al and Orenstein et al included infants with symptomatic GORD. Omari et al also required 24-hour pH monitoring. Davidson et al included those with more than one of the following: apnoea, vomiting or gagging and irritability or pain. Wheatley et al required a clinical diagnosis of GORD and bradycardia attributed to GOR, as well as 2 episodes of bradycardia per day and Corvaglia (a) et al specifically required subjects to have recurrent postprandial apnoeas.

None of the studies reported on the prespecified secondary outcomes, namely: time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis and suspected or proven sepsis. Orenstein et al looked at treatment-emergent adverse events and serious adverse events including upper respiratory tract infections, constipation, dermatitis, ear infections, fever, lower respiratory tract infection, respiratory tract congestion, rhinorrhoea, candidiasis, diarrhoea (excluding infective), vomiting, alkaline phosphatase increase, and others.

Effects of Interventions

Sodium Alginate (Gaviscon) vs Placebo

There was significant decrease in total GORs, pH-GORs, aMII-GORs, RIpH and Proximal GORs. [11, 12] (Table 2)

Table 2. Effect of Alginates (Gaviscon) use in preterm infants

Studies	Antacids	Control	P
Corvaglia (a) et al			
Total GORs	49.00 (28.50–67.00)	58.50 (33.50–75.75)	0.024
Liquid GORs	21.50 (12.25–32.00)	21.50 (13.50–39.75)	0.432
Gaseous GORs	2.00 (0.25–7.50)	3.00 (0.00–14.75)	0.040
Mixed GORs	3.00 (2.00–5.75)	3.00 (1.00–5.00)	0.614
pH-GORs	17.00 (6.00–29.75	29.00 (13.50–44.50)	0.002
aMII-GORs	4.00 (2.00–8.25)	6.00 (2.25–11.75)	0.050
NaMII-GORs	19.00 (10.00–32.75)	18.50 (8.50–33.75)	0.743
RIpH	4.0 (1.8–13.1)	7.6 (3.3–17.0)	0.030
aMII-GOR-BEI	0.2 (0.1–0.6)	0.4 (0.1–1.0)	0.036
NaMII-GOR-BEI	1.2 (0.5–1.9)	0.9 (0.5–1.7)	0.822
Distal GORs (no.)	18.00 (11.25–27.00	15.00 (9.25–26.00)	0.959
Proximal GORs (no.)	5.50 (4.00–9.00)	7.50 (3.00–12.00)	0.030
Corvaglia (b) et al			
Total GOR episodes	9 (0–33)	20.5 (1–42)	0.001
pH-GOR	2 (0–26)	7.5 (0–23)	0.004
a-MII-GOR	1 (0–5)	3 (0–16)	0.001
Na-MII-GOR	4.5 (0–22)	6 (1–21)	0.145
RIpH	0.9 (0–23.2)	8.4 (0–44.2)	0.001
a-MII-BEI	0.17 (0–2)	0.5 (0–8.1)	0.002
Na-MII-BEI	0.75 (0–5.7)	1.0 (0.1-9.2)	0.982

GOR: Gastro-Oesophageal Reflux;MII: multichannel intraluminal impedance monitoring; pH-GOR: GOR episodes detected only by pH monitoring; aMII-GOR: acid GOR episode detected by MII; NaMII-GOR: non-acid GOR episode detected by MII; RIpH: Reflux Index detected only by pH monitoring; aMII-GOR-BEI: acid MII-GOR-bolus exposure index; NaMII-GOR-BEI: non-acid MII-GOR-bolus exposure index

Esomeprazole vs Placebo

No significant results were obtained from this study which was discontinued prematurely due to poor enrolment. [14](Table 3)

Table 3. Effect of Proton Pump Inhibitors use in preterm infants

Studies	Antacids	Control	P
Esomeprazole vs Placebo			
Davidson et al			
Total number of GORD-related signs and symptoms (percentage of change from baseline after 14 days of treatment)	-14.7%	14.1%	0.92
Gastrointestinal events	-8.39%	10.16%	0.42
Neurobehavioral events	-3.54%	-3.98%	0.94
Cardiorespiratory events	-38.94%	-41.17%	0.89
Omeprazole vs Placebo			
Omari et al			
Gastric acidity (%time pH<4)	13.9 ± 5.1	53.8 ± 6.8	<0.0005
Oesophageal acid exposure (%time pH<4)	4.9 ± 3.4	19.0 ± 4.5	<0.01
No. of acid GOR episodes	119.4 ± 20.	59.6 ± 26.7	<0.05
No. of oesophageal acid GOR >5min	8.0 ± 2.1	3.0 ± 2.0	<0.01
Lansoprazole vs Placebo			
Orenstein et al			
Primary efficacy: Responder rate, n (%)	44 (54%)	44 (54%)	NS
AEs	50 (62%)	37 (46%)	NS
SAEs	10 (12%)	2 (2%)	0 .032

GORD: Gastro-Oesophageal Reflux disease; GOR: Gastro-Oesophageal Reflux; NS, not significant; AEs: adverse events; SAEs: serious adverse events.

Omeprazole vs Placebo

Analyses on the basis of pH recordings showed that Omeprazole therapy significantly reduced the oesophageal acid exposure % time pH<4 (omeprazole vs placebo, mean ± standard error mean, 4.9 ± 3.4 vs 19.0 ± 4.5, paired t-test P<0.01) and reduced gastric acidity % time pH<4 (13.9 ± 5.1 vs 53.8 ± 6.8, P<0.0005). [10](Table 3)

There were no significant changes to symptom frequency (vomiting, apnoea, bradycardia, choking, behavioural changes) or blood results.

Lansoprazole vs Placebo

No significant results were obtained from this trial, 54% of infants in both double-blind groups responded to intervention. [13] (Table 3)

Metoclopramide and Ranitidine vs Placebo

18 patients were enrolled, and 17 completed the study, with a gestational age of 29 ± 3 weeks. There was a significant decrease in the number of bradycardia episodes per day in the mean combined placebo time periods compared to the mean combined drug time periods [3.6 (SD 2.7) vs 4.6 (SD 3.1)), P = 0.04], and in bradycardia episodes over time (P<0.001), with fewer episodes during placebo periods. [9]

DISCUSSION

This systematic review demonstrates the lack of efficacy and safety data for anti-GORD drug therapy in preterm infants. The heterogeneity of the interventions precluded a meta-analysis.

Alginates

Corvaglia (a) and (b) et al. found that sodium alginate significantly decreased the number of acid gastro-oesophageal reflux detected either by pH and impedance monitoring, and also acid oesophageal exposure, without any influence on non-acid gastro-oesophageal reflux.

However, sodium alginate didn't reduce the total number of apnoea of prematurity nor GOR-related apnoeas.[12]

Furthermore, sodium alginate was found to lower the number of GORs reaching the proximal oesophagus and also the number of gaseous GORs. Corvaglia (a) et al reports that participants were observed over a 24 hour period, and data was collected after 8 meals, whereas in Corvaglia (b) participants were observed over 9 hours, and data was collected after 2 meals. It is possible that the authors of Corvaglia (b) et al chose only to report data from the 9 hour period, instead of using the full 24 hour data, in order to report more significant results. This discrepancy diminishes the validity of the papers and suggests that the evidence should not be applied to clinical practice.

Proton pump inhibitors

Omari et al. showed that 0.7 mg/kg omeprazole given once daily was effective in reducing the frequency of acid reflux episodes and the overall degree of oesophageal acid exposure in premature infants. The drug-dosing regimen used appeared safe based on adverse event reporting and blood screening. However, due to the small number of participants enrolled in the study (n=10), it would be difficult to state whether this evidence is applicable in everyday practice and more trials must be carried out into the effectiveness of omeprazole.

There were no significant differences in the number of GORD-related signs and symptoms between neonates receiving esomeprazole or lansoprazole vs placebo.[13, 14]

Serious AEs, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo group (10 vs 2; P= .032); There was a 35% loss of follow up for participants receiving lansoprazole and 36% for participants receiving placebo. It is unclear whether this caused a significant imbalance in characteristics between the two interventions. Therefore, applicability into everyday practice is low because loss to follow-up can severely compromise validity as those lost to follow-up could have a different prognosis than those who

complete the study. The number of AEs was similar between neonates receiving esomeprazole vs placebo.

H2-receptor antagonists

A retrospective cohort study conducted by Romainea et al. [15] in USA concluded that H2 blocker use was associated with increased risk of the combined outcome of death, NEC, or sepsis in hospitalized VLBW infants. Another recent retrospective cohort study showed that ranitidine use was associated with an increased risk of infections and mortality in preterm infants, but not with NEC.[16]

Wheatley showed that ranitidine did not reduce, and may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GOR. Wheatley compared the combination of 2 interventions together against a placebo, ranitidine, a H2 receptor antagonist and metoclopramide, a dopamine receptor antagonist. With regards to applicability, the data derived from this study actually suggests that combining ranitidine and metoclopramide may be detrimental to patients and should therefore be avoided in clinical practice, as it showed a significant increase in bradycardia episodes during drug periods. This may be caused by significant interactions between the 2 drugs that could either decrease the efficacy of either or both of drugs or perhaps cause adverse effects. Leucuta et al, found pharmacokinetic changes, such as an increased half-life, in metoclopramide, when taken with ranitidine.[17] However, it is quite likely that this is a chance finding, given the small number of participants enrolled in the study (n=18). Previous studies into the combined effectiveness of ranitidine and metoclopramide suggest that this treatment is effective at increasing gastric pH and reducing the side effects of GORD, and do not mention any significant drug induced side effects or drug interactions.[18,19]

Summary of main results

Omeprazole was successful in reducing gastric and oesophageal pH, but not the symptoms associated with GORD, which may imply that omeprazole had little effect on non-acid GOR episodes. The combined use of ranitidine and metoclopramide actually proved counter-effective,

with placebo periods giving significantly less bradycardia episodes than drug periods. Sodium alginate significantly reduced GOR episodes, though had no effect on the reduction of apnoeas. Esomeprazole and Lansoprazole appeared to have no significant effect on symptoms of GORD.

Limitations

Not all studies met the inclusion criteria outlined in the methods. We initially stated that only preterm infants <37 weeks gestation were to be included in this review, however both Davidson et al and Orenstein et al included data for full-term infants as well as preterm, some of whom were >37 weeks gestation. Authors were contacted to obtain exclusively preterm data, however, replies were not received. We included these studies in this review due to the high percentage of preterm infants enrolled in the trials. The methods stated that the only interventions that were to be considered were H2 receptor antagonists, proton pump inhibitors and alginates, however Wheatley et al assessed the combined effects of both metoclopramide (dopamine receptor antagonist) and ranitidine (H2 receptor antagonist). We still decided to report this outcome as the inclusion of the H2 receptor antagonist as it is of interest to the reader in general who must bear in mind this was a combined intervention.

Agreements or disagreements with other studies or reviews

To our knowledge, this review is the first to look into the effects of antacids in preterm infants. Terrin et al. in a retrospective study of 274 very low birth weight infants reported that the risk of necrotizing enterocolitis, nosocomial infection and mortality were significantly higher in the infants exposed to ranitidine.[4] However, non-prospective, non-controlled and un-blinded design features limited its significance. A Cochrane review by Tighe et al looking at the effects of pharmacological treatment for the management of GORD in children concluded that although there is evidence to support pharmacological use in older children, use in infants is unsupported due to lack of robust RCT evidence.[20]

Cohen et al. in a recent review suggested that the use of GORD medications should only be used after non-pharmacological measures have been taken with incomplete success as acid

suppression may place immune-deficient infants and children at risk for the development of lower respiratory tract infections and nosocomial sepsis. [21]

Author's Conclusions

There is insufficient evidence on the efficacy and safety of antacids in preterm infants. The lack of research in this area of medicine is a problem that must be addressed in this population of patients. Adequately powered, randomised, controlled trials in preterm infants are needed to determine the safety and effectiveness of these commonly used medications.

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Study concept and design: Dr. Dorling and Dr. Schoonakker conceived and designed the study.

Acquisition of data: Dr. Mackie and Dr. Dermyshi.

Analysis and interpretation of data: Dr. Dermyshi, Dr. Mackie, Dr. Kigozi, Dr Schoonakker and Dr. Dorling.

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References

1. Corvaglia L, Monari C, Martini S, et al. Pharmacological therapy of gastroesophageal reflux in preterm infants. *Gastroenterol Res Pract*. 2013; 2013:714564. doi: 10.1155/2013/714564.

2. Rossor T, Andradi G, Bhat R Greenough A. Investigations and management of gastro-oesophageal reflux in United Kingdom neonatal intensive care units Acta Paediatrica 2018 January; DOI:10.1111/apa.14073.

3. Guillet R, Stoll BJ, Cotten CM, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; 117(2):e137-42.

4. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012 Jan;129(1):e40-5. doi: 10.1542/peds.2011-0796.

5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009 Oct; 62(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006.

6. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (updated March 2011). *The Cochrane Collaboration* 2011 (Available at: www.cochrane-handbook.org.).

7. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011 Oct 18; 343:d5928. doi: 10.1136/bmj.d5928.

8. Guyatt G, Oxman AD, Akl EA, et al: GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011 Apr; 64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026.

9. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr*. 2009 Oct; 155(4):516-21. doi: 10.1016/j.jpeds.2009.03.044.

10. Omari TI, Haslam RR, Lundborg P, et al. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. *Journal of pediatric gastroenterology and nutrition* 2007; 44(1):41-4.

11. (a) Corvaglia L, Aceti A, Mariani E, et al. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants. *Aliment Pharmacol Ther.* 2011 Feb; 33(4):466-70. doi: 10.1111/j.1365-2036.2010.04545.x.

12. (b) Corvaglia L, Spizzichino M, Zama D, et al. Sodium Alginate (Gaviscon(R)) does not reduce apnoeas related to gastro-oesophageal reflux in preterm infants. *Early Hum Dev.* 2011 Dec; 87(12):775-8. doi: 10.1016/j.earlhumdev.2011.05.013.

13. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr.* 2009 Apr; 154(4):514-520.e4. doi: 10.1016/j.jpeds.2008.09.054.

14. Davidson G, Wenzl TG, Thomson M, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *J Pediatr.* 2013 Sep; 163(3):692-8.e1-2. doi: 10.1016/j.jpeds.2013.05.007.

15. Romainea A, Ye D, Ao Z, et al. Safety of Histamine-2 Receptor Blockers in Hospitalized VLBW Infants. *Early Hum Dev.* 2016 Aug; 99:27-30. doi: 10.1016/j.earlhumdev.2016.05.010.

16. Santana RNS, Santos VS, Ribeiro-Júnior RF, et al. Use of ranitidine is associated with infections in newborns hospitalized in a neonatal intensive care unit: a cohort study. *BMC Infect Dis.* 2017 May 30; 17(1):375. doi: 10.1186/s12879-017-2482-x.

17. Leucuţa A, Vlase L, Farcău D, et al. Pharmacokinetic interaction study between ranitidine and metoclopramide. *Romanian journal of gastroenterology* 2004; 13(3):211-4.

18. Hong J-Y. Effects of Metoclopramide and Ranitidine on Preoperative Gastric Contents in Day-Case Surgery. *Yonsei Medical Journal* 2006; 47(3):315-318. doi:10.3349/ymj.2006.47.3.315.

19. Bala I, Prasad K, Bhukal I, Nakra D, Pratap M. Effect of preoperative oral erythromycin, erythromycin-ranitidine, and ranitidine-metoclopramide on gastric fluid pH and volume. *J Clin Anesth.* 2008 Feb; 20(1):30-4. doi: 10.1016/j.jclinane.2007.08.002.

20. Tighe M, Afzal NA, Bevan A, et al. *Cochrane Database Syst Rev*. 2014 Nov 24; (11):CD008550. doi: 10.1002/14651858.CD008550.pub2.

21. Cohen S, Bueno de Mesquita M, Mimouni FB. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. *Br J Clin Pharmacol.* 2015 Aug; 80(2):200-8. doi: 10.1111/bcp.12619.

Tables

Figures

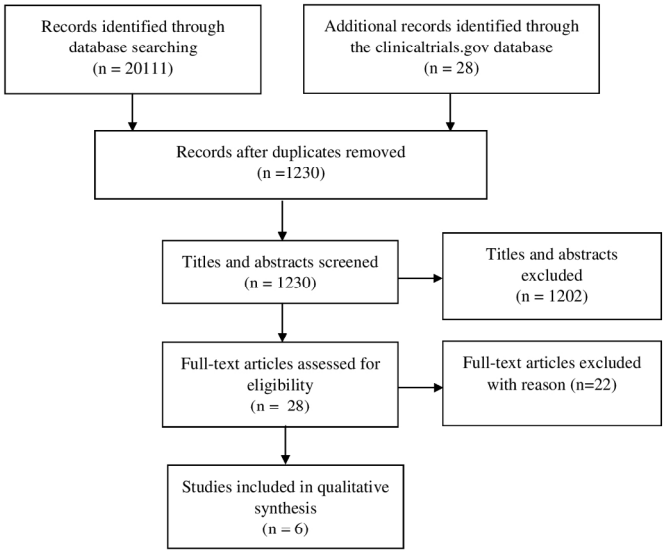

Figure 1: Study flow diagram

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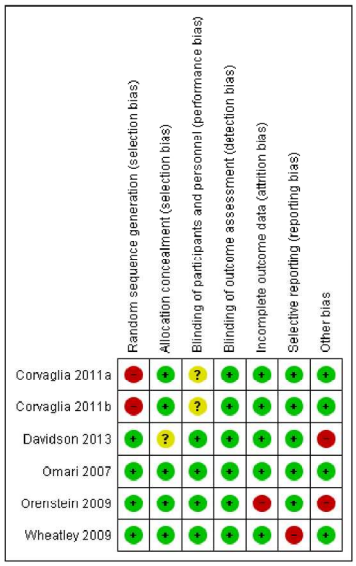

Figure 2 – Risk of Bias Summary

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Appendix 1 Search strategies

Search Methods for Identification of Studies

The standard search of the Cochrane Neonatal Review Group, including electronic searches of the Cochrane central register of controlled trials (CENTRAL, The Cochrane Library), MEDLINE (1966 – to present), EMBASE (1980- to present) and CINAHL (1982 –to present) was used. There was no language restriction applied.

The following search terms were applied for each database:

- Cochrane Library: There were total **864** results for: gastroesophageal reflux in All Fields AND infant in All Fields AND preterm in All Fields AND antacid in All Fields **3** reviews and **30** RCTs
- PubMed: Total **4195** ("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])

  24 (("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND ("Trials"[Journal] OR "trials"[All Fields]) AND Clinical Trial[ptyp]

  4 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND ("Trials"[Journal] OR "trials"[All Fields]) AND Clinical Trial[ptyp]) AND ("antacids"[Pharmacological Action] OR "antacids"[MeSH Terms] OR "antacids"[All Fields] OR "antacid"[All Fields]) AND Clinical Trial[ptyp]

    180 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields]))) AND preterm

    3 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("omeprazole"[MeSH Terms] OR "omeprazole"[All Fields] OR "esomeprazole"[MeSH Terms] OR "esomeprazole"[All Fields])

    2 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND (("receptors, histamine h2"[MeSH Terms] OR ("receptors"[All Fields] AND "histamine"[All Fields] AND "h2"[All Fields]) OR "histamine h2 receptors"[All Fields] OR ("h2"[All Fields] AND "receptor"[All Fields]) OR "h2 receptor"[All Fields]) AND ("antagonists and inhibitors"[Subheading] OR

("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "antagonists"[All Fields]))

3 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AORND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("ranitidine"[MeSH Terms] OR "ranitidine"[All Fields])

11 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("proton pump inhibitors"[Pharmacological Action] OR "proton pump inhibitors"[MeSH Terms] OR ("proton"[All Fields] AND "pump"[All Fields] AND "inhibitors"[All Fields]) OR "proton pump inhibitors"[All Fields])

3 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("omeprazole"[MeSH Terms] OR "omeprazole"[All Fields] OR "esomeprazole"[MeSH Terms] OR "esomeprazole"[All Fields])

1 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("lansoprazole"[MeSH Terms] OR "lansoprazole"[All Fields])

2 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("pantoprazole"[Supplementary Concept] OR "pantoprazole"[All Fields])

1 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("rabeprazole"[MeSH Terms] OR "rabeprazole"[All Fields])

1 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("esomeprazole"[MeSH Terms] OR "esomeprazole"[All Fields])

6 ((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields])) AND preterm[All Fields]) AND ("alginates"[MeSH Terms] OR "alginates"[All Fields])

8 (((((("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields]))) AND preterm)) AND antacid

- Embase: Search terms used: antacid: **14892** text results; limit 1 to infant <to one year> 54 text results; limit 2 to clinical trial; 3 text results

- Wiley Online Library: There were **102** results for: gastroesophageal reflux in All Fields AND infant in All Fields AND preterm in All Fields AND antacid in All Fields

- Cinahl: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

A database search of clinicaltrials.gov was also carried out, for ongoing and completed trials, using the search terms infant or preterm AND reflux or gastroesophageal reflux showed **28** results.

The reference list of included studies and previous relevant reviews was analysed. Trials reported as abstracts or letters to the editor were included if sufficient data was presented within the report, or if authors could be contacted, to fulfil the inclusion criteria.

Appendix 2

sTable 1 – Characteristics of Excluded Studies

Excluded Study	Reason for Exclusion
Abdel-Rahman 2004	Not a RCT; uses different doses of Nizatidine
Adamko 2012	Exclude as infants with cough and wheeze.
Atasay 2010	Not a RCT.
Cresi 2006	Not a RCT
Dhillon 2004	Not a RCT
Golski 2010	Not a RCT
Kierkus 2011	Not a RCT, compared 2 different doses of Pantoprazole
Le 1992	Not a RCT, compared 2 different doses of Alginate
Loots 2014	States that patients have been 'referred' so assumed that these are GP patients and not preterm infants.
Omari 2009	Not a RCT.
Orenstein 2005	Comparison of 2 doses of Nizatidine
Sandstrom 2012	Not a comparative RCT v placebo (different doses of esomeprazole)
Springer 2008	Not a RCT.
Sutphen 1986	Not a RCT
Tammara 2011	Compared 2 doses of pantoprazole, did not use placebo.
Ward 2010	Compares 2 doses of pantoprazole
Weldon 1972	Not a RCT
Wenning 2005	Not a RCT
Zhang 2008	Not a RCT
Slaughter 2016	Not RCT
Santana 2017	Not RCT
Romaine 2016	Not RCT

Appendix 3

Risk of bias in included studies

When assessing the quality of RCTs, bias is a very important consideration. We have looked at the various areas where bias may arise throughout the trials and given this an overall level of risk.

Selection

Allocation was randomised with Davidson et al using block randomisation, and with Omari et al, Orenstein et al and Wheatley et al using a random number generator. Corvaglia (b) et al and Corvaglia (a) et al did not report any form of random sequence generation for allocation. With regards to allocation concealment, Davidson et al is unclear about its methods of concealment.

Performance

Davidson et al, Omari et al, Orenstein et al and Wheatley et al all state or imply that their placebo was prepared and appeared similar to the drug, thus ensuring the blinding of participants and personnel. Corvaglia (b) et al and Corvaglia (a) et al were not clear about their methods taken to ensure blinding.

Detection

Data were assessed by independent assessors for Corvaglia (b) et al, Corvaglia (a) et al, Davidson et al and Wheatley et al minimising risk of detection bias. No apparent detection bias was found in Omari et al and Orenstein et al.

Attrition

Corvaglia (a) et al, Corvaglia (b) et al and Omari et al reported all outcomes. Davidson et al and Wheatley et al both lost 1 participant each to follow-up during the study; Davidson et al was due to efficacy data not being available, Wheatley et al does not give an explanation. 57 of 162 participants in Orenstein et al discontinued the treatment early giving a high risk of attrition bias. 55 of these participants went on to take open-label lansoprazole, the results of which were reported and incomplete data was carried forward to the 4th week for the double-blind results. It is unclear what happened to the remaining 2 participants.

sTable 2 – Risk of Bias Table – Corvaglia (b) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	High Risk	The DG ('drug-given') meal was randomly chosen in order to avoid any possible carry-over effect. As same study as Corvaglia (a) et al, it seems this was a random choice of data from 2 DG ('drug-given') and DF ('drug-free') feed in a 9 hour window.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	The investigator was blind to the administration of sodium alginate. pH-MII and PSG data were analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

sTable 3 - Risk of Bias Table - Corvaglia (a) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	High Risk	Each patient assessed over 24 hour period; 8 feeds with 2nd, 4th, 6th and 8th feed was DG ('drug-given') meal. No randomisation used.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	During layout analysis the investigator was blind to the administration of sodium alginate. pH-MII and PSG data were then analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

sTable 4 – Risk of Bias Table – Davidson et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A block randomisation scheme was used, stratified by centre.
Allocation concealment (selection bias)	Unclear Risk	Method of randomisation allocation not clearly described.
Blinding of participants and personnel (performance bias)	Low Risk	Treatments blind to all, method described but not explicit that the active and placebo preparations looked identical.
Blinding of outcome assessment (detection bias)	Low Risk	Two blinded central readers independently reviewed the videos and cardiorespiratory data.
Incomplete outcome data (attrition bias)	Low Risk	One patient in the placebo group completed the study, but was lost to follow-up between study completion and the safety follow-up visit.
Selective reporting (reporting bias)	Low Risk	One patient in the esomeprazole group was excluded from the modified ITT analysis because of invalid efficacy measurements.
Other bias	High Risk	Sponsored by AstraZeneca LP (Wilmington, Delaware). AstraZeneca was involved in the design and conduct of the study; collection, analysis, and interpretation of the data; and the preparation, review, and approval of the trial report manuscript. 2 authors, both funded by AstraZeneca developed the first draft of the trial report manuscript. 3 employees of AstraZeneca, included work on this manuscript among their job responsibilities and also had limited AstraZeneca stock ownership. 3 authors had received grants and research support from AstraZeneca.

sTable 5 - Risk of Bias Table – Omari et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A stock solution containing either 5mg/mL omeprazole or sterile water was prepared and dispensed by pharmacy according to a randomisation schedule determined using a random number generator.
Allocation concealment (selection bias)	Low Risk	Drug or placebo prepared and dispensed using random number generator.
Blinding of participants and personnel (performance bias)	Low Risk	A stock solution was prepared which contained either omeprazole or sterile water (placebo). It is not clear how similar these were.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent detection possible.
Incomplete outcome data (attrition bias)	Low Risk	Follow up data complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	AstraZeneca R&D Molndal assisted by performing plasma omeprazole assays.

sTable 6 - Risk of Bias Table – Orenstein et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Double-blind treatment assignments were made through a central web-based system according to a schedule that was computer generated.
Allocation concealment (selection bias)	Low Risk	States that treatment assignments were concealed to study personnel
Blinding of participants and personnel (performance bias)	Low Risk	Appearance, reconstitution, and administration of lansoprazole and placebo were identical.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent bias in outcome assessment.
Incomplete outcome data (attrition bias)	High Risk	55 of 162 discontinued treatment early for open label treatment. For such subjects, the last week of available data was carried forward to 4th week for the individual symptoms and global severity assessments.
Selective reporting (reporting bias)	Low Risk	All randomised infants administered 1 or more dose(s) of study drug were included in the intention-to-treat data set for efficacy and safety analyses.
Other bias	High Risk	Takeda Global Research & Development Center, Inc sponsored the clinical trial, employed 2 authors and data interpretation and analysis was also undertaken by their employees.

sTable 7 – Risk of Bias Table – Wheatley et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Study group assignment (order of medication and placebo administration) was determined by blocked random number generation.
Allocation concealment (selection bias)	Low Risk	A research pharmacist assigned the study group for each patient at the time of enrolment.
Blinding of participants and personnel (performance bias)	Low Risk	Investigators, clinicians, and parents were all blind to the group assignment during the study period. Intravenous preparations were used because they were clear and colourless. Saline placebos of the same volume and colour were administered during the placebo periods.
Blinding of outcome assessment (detection bias)	Low Risk	At the end of the study period for each infant, after the study outcome data were summarised for the infant, the investigator contacted the pharmacist to ascertain the group assignment (order of medication and placebo administration) for the infant, eliminating bias as data were analysed prior to finding out group assignment.
Incomplete outcome data (attrition bias)	Low Risk	One infant was enrolled in the study but was then withdrawn, with no explanation for the withdrawal.
Selective reporting (reporting bias)	High Risk	Clinicaltrials.gov record shows that the authors originally planned to analyse and present data on apnoea also. This was not included and the protocol was changed on clinicaltrials.gov.
Other bias	Low Risk	No conflicts of interest or sponsorship.

Appendix 4

sTable 8: Summary of findings: Antacid in preterm infants

Antacid compared to placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants

Intervention: Antacid

Comparison: placebo or standard care

Outcomes	Medication	Effect	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
Improvement in symptom score	Alginate	**Weak evidence** of efficacy was found for Sodium Alginate (Gaviscon) – 60 infants (2 studies)	474 children (9 studies)	⊕◯◯◯ Very LOW[1,2,3,4]	
	Proton pump inhibitors	**Weak evidence** of efficacy was found for Omeprazole-10 infants (1 study), Lansoprazole-162 infants (1 study) and Esomeprazole-52 infants (1study)			
	H2 receptor antagonists	**No evidence** of efficacy was found for Ranitidine – 18 infants (1 study).			
Adverse events	Alginate	No adverse event was recorded during the study period.	474 children (9 studies)	⊕◯◯◯ Very LOW[1,2,3,4]	
	Proton pump inhibitors	Treatment-emergent serious AEs (SAEs), particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo group. 4 SAEs (neonatal bradycardia, cyanosis, inappropriate device signal detection, and infantile apnoeic attack) were reported in 3 placebo patients and no SAEs were reported in the esomeprazole-treated patients.			

sTable 8: Summary of findings: Antacid in preterm infants

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Patient or population: preterm infants

Intervention: Antacid

Comparison: placebo or standard care

Outcomes	**Medication**	**Effect**	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	H2 receptor antagonists	There were no adverse effects attributed to ranitidine. However , it may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GER.			

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix 5

sTable 9 – Study outcomes

	Corvaglia et al, 2011(b)	Corvaglia et al, 2011(a)	Davidson et al, 2013	Omari et al, 2007	Orenstein et al, 2009	Wheatley et al, 2009
Oesophageal pH				✓		
Gastric pH				✓		
Total GOR episodes	✓	✓				
Bradycardia			✓	✓		✓
Apnoea	✓		✓	✓		
Choking/coughing			✓	✓	✓	
Vomit/Reguritations			✓	✓	✓	
Back arching	✓		✓			
Oxygen Desaturation			✓			
Behavioural/Crying			✓	✓	✓	

BMJ Paediatrics Open

Antacid therapy for gastroesophageal reflux in preterm infants:
A Systematic Review

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Keywords:	Neonatology, Infant Feeding

Antacid therapy for gastroesophageal reflux in preterm infants:

A Systematic Review and Qualitative analysis

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Word count: 2488

Short title: Antacid therapy for gastroesophageal reflux in preterm infants

PROSPERO registration number: CRD42017078778 (www.crd.york.ac.uk/PROSPERO; ref CRD42017078778).

Abbreviations:

H2 Ras: Histamine-2 receptor antagonists;

PPI: Proton Pump Inhibitors;

GORD: Gastro-Oesophageal Reflux disease;

GOR: Gastro-Oesophageal Reflux;

AEs: adverse events;

SAEs: serious adverse events;

NEC: Necrotising enterocolitis;

RCTs: Randomized controlled trials;

DG: Drug-given;

DF: Drug-free;

MII: multichannel intraluminal impedance monitoring;

pH-GOR: GOR episodes detected only by pH monitoring;

aMII-GOR: acid GOR episode detected by MII;

NaMII-GOR: non-acid GOR episode detected by MII;

RIpH: Reflux Index detected only by pH monitoring;

aMII-GOR-BEI: acid MII-GOR-bolus exposure index;

NaMII-GOR-BEI: non-acid MII-GOR-bolus exposure index.

VLBW infants: very low birth weight infants

Abstract

Background

Gastroesophageal reflux is prevalent in preterm infants. Despite widespread use in clinical practice, there is still much controversy over the efficacy and safety of pharmacological interventions, particularly antacid therapy.

Objective

To systematically review the effects of antacid therapy on preterm infants with symptoms of gastroesophageal reflux, and to assess the safety of these interventions.

Methods

We carried out an electronic search of the Cochrane central register of controlled trials (CENTRAL, The Cochrane Library), MEDLINE (1966 – to present), EMBASE (1980- to present) and CINAHL (1982 –to present) as well as other online sources. Participants were preterm infants (<37 weeks gestation) with gastroesophageal reflux disease who were receiving care on a neonatal unit. We assessed the effects of H2 receptor antagonists, PPIs and alginates against placebo, primarily to see if they reduced the symptoms of reflux.

Results

6 studies were included in this review. Meta-analysis could not be carried out due to a lack of studies assessing the same intervention with the same outcomes. Omeprazole therapy significantly reduced the oesophageal acid exposure percentage time with pH<4 ($p<0.01$) and sodium alginate significantly decreased GOR episodes ($p=0.024$). Metoclopramide and ranitidine showed a significant increase in GORD symptoms versus placebo ($p<0.04$). No significant results were found for the use of esomeprazole or lansoprazole versus placebo.

Conclusions

There is insufficient evidence available to conclude whether antacid therapy is effective or safe when treating GORD in preterm infants. Further research is needed into this topic and caution must be taken when administering antacids to preterm infants.

Systematic review registration number: CRD42017078778

Keywords: systematic review; gastroesophageal reflux disease; oesophageal reflux or oesophageal reflux; antacids; histamine receptor antagonists; proton pump inhibitors; alginate; preterm; infant; low birth weight.

What is known?

- Gastroesophageal reflux is a prominent condition among preterm infants.
- Pharmacological interventions are often used to treat GORD, despite the lack of good quality evidence to support its use.
- Studies have shown a significant positive correlation between the use of H2 RAs and important complications.

What is new?

- There is limited evidence supporting the use of antacids in preterm infants
- Omeprazole reduced gastric and oesophageal pH, but did not alter GORD symptoms. Esomeprazole and Lansoprazole had no significant effect on GORD signs and symptoms.
- Combined use of ranitidine and metoclopramide appears counter-effective, with placebo periods giving less bradycardia episodes versus drug periods.

Background

Gastroesophageal reflux is a prominent condition among preterm infants. Despite this, controversy remains over how it should be treated. Currently, non-pharmacologic therapies are generally the first line of treatment in GORD, with pharmacological interventions reserved for those who do not respond .[1]Antacids containing alginate, Histamine-2 receptor antagonists (H2 RAs) and proton pump inhibitors (PPI) are among the most common interventions used with 60%, 53% and 23% of UK neonatal units using these products respectively. [2]

Studies have also shown a significant correlation between the use of H2RAs and important complications. [3, 4] Guillet et al showed H2-blocker use was associated with an increased incidence of NEC (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.34–2.19; P < .0001).

There continues to be a widespread use of the pharmacology therapies in neonatal units today despite the evidence gaps. This review was carried out to systematically evaluate the evidence of efficacy and safety of antacid treatment for GORD in preterm infants and to highlight potential areas for future research.

Objectives

Primary objective:

To assess the effectiveness of antacid therapy in preterm infants diagnosed with gastroesophageal reflux disease.

Secondary objective:

To assess the safety of antacid therapy in preterm infants diagnosed with gastroesophageal reflux disease.

MATERIAL AND METHODS

We used Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Cochrane Handbook of Systematic Reviews of Interventions approach for conducting and reporting systematic reviews and meta-analyses of randomized controlled trials (RCTs).[5,6] The methodology of this systematic review was published in PROSPERO (www.crd.york.ac.uk/PROSPERO; ref CRD42017078778).

Search methods for identification of studies

MEDLINE/PubMed, Embase, Wiley Online Library, Cochrane Library and Web of Science databases were searched to identify trials of antacid therapy in preterm infants. Databases were screened for publications from the earliest available date until October 15, 2017. No language restrictions were applied. Ethical approval was not required because only published articles were included in this review. A database search of clinicaltrials.gov for ongoing and completed trials was also carried out, using the search terms infant or preterm and reflux or gastroesophageal reflux. Trials reported as abstracts or letters to the editor were included if sufficient data to fulfil the inclusion criteria was presented within the report, or provided by authors. Full search strategy is presented in supplementary Appendix 1.

Eligibility criteria

All relevant randomised trials involving preterm infants (<37 weeks gestation) with GORD (clinical diagnosis and/or 24-hour intraoesophageal PH monitoring, or impedance studies) receiving care on a neonatal unit. Crossover, randomised trials or Quasi-randomised studies, described in some way as to suggest or imply that the study was randomised if the demographic detail of each group was similar were included.

Types of interventions

All available antacid therapies for gastro-oesophageal reflux in neonates were included. Antacid therapy (administered by any method) should have been commenced after the diagnosis of GORD and continued for any duration.

The interventions considered were:

- H2 receptor antagonists versus a placebo or standard care.
- Proton pump inhibitors versus a placebo or standard care.
- Alginates versus a placebo or standard care.

Trials were not limited by dose, frequency or duration of intervention.

Selection of studies

Paired reviewers (ED, CM, BS, JD) independently screened titles, abstracts and then full texts for eligibility, assessed risk of bias, and collected data from included studies. Any disagreement between reviewers was resolved through discussion or adjudication by a third reviewer (BS, JD). In case of duplicate publications, the most recent and updated report of the study was included. When necessary, further information was obtained from study authors.

Risk of bias and quality of evidence assessment

The Cochrane Risk-of-Bias Tool was used to assess the risk of bias. [7] The quality of the evidence of outcomes was rated by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8]

Data extraction

From each eligible study the following information was collected: study characteristics (e.g., author name, year of publication, sample size, patient characteristics, antacid type, duration of intervention, dosage, and at least one clinical outcome.

Primary outcomes

- A reduction in reflux symptoms assessed by a reflux index score or clinical symptoms score.

Secondary outcomes

- Time taken to establish full enteral feeds
- Length of hospital stay
- Necrotising enterocolitis (Bell's stage 2 or greater)
- Suspected or proven sepsis
- Other adverse effects

Results

Description of Studies

A total of 20111 articles were identified by the initial search. 18881articles were excluded as duplicates, meta-analysis or other reasons. Thus, 1230 were potentially eligible after title and abstract screening, and 6 studies met our inclusion criteria. (Figure 1) Records identified through the clinicaltrials.gov database were not included as they were either incomplete or did not fit the selection criteria.

All included studies were double-blind, randomised, placebo-controlled trials. 4 of the 6 were cross-over trials (Wheatley et al[9], Omari et al[10], Corvaglia (a) et al[11], Corvaglia (b) et al[12]), whilst the remaining 2 were parallel trials (Orenstein et al[13], Davidson et al[14]).

The main characteristics of included RCTs are described in Table 1 and excluded studies are summarized in supplementary appendix 2.

Table 1 - Characteristics of Included Studies

Studies	Corvaglia (a) et al[11]	Corvaglia (b) et al[12]	Davidson et al[14]	Omari et al[10]	Orenstein et al[13]	Wheatley et al[9]
Methods	Clinical trial - cross-over of treatment and placebo	Clinical trial - cross-over of treatment and placebo	Randomised, double blind, placebo controlled trial	Randomised, controlled, double-blind trial - crossover design	Randomised Controlled Trial - multicentre, double-blind, parallel-group study	Randomised, controlled, masked cross-over study
Participants	32 Preterm newborns (gestational age ≤33 weeks) with symptoms of GOR (frequent regurgitations and/or postprandial desaturations)	28 Preterm newborns (gestational age ≤33 weeks) with recurrent postprandial apnoeas.	52 Term infants or with a gestational or post-conceptional age of 28 to 44 weeks	10 Preterm infants with a mean postmenstrual age of 36.1 ± 0.7 (range, 34-40 weeks)	162 Infants aged 16 weeks (median, range 4-51) gestation at birth 35 weeks (median, range 25-39)	18 Preterm infants having >3 bradycardia episodes per 2 days
Interventions	0.25 ml/kg sodium alginate was given four times at alternate meals ('drug-given' (DG) meals), remaining four meals were placebo ('drug-free' (DF) meals)	0.25 ml/kg sodium alginate after one single meal ("drug given" meal) or placebo ("drug free" meal)	Esomeprazole 0.5 mg/kg or placebo	0.7mg/kg omeprazole once daily or placebo	Lansoprazole administered once daily at 0.2 to 0.3 mg/kg/day for infants age ≤10 weeks and at 1.0 to 1.5 mg/kg/day for those age >10 weeks or placebo administered identically but without active drug.	Metoclopramide, 0.2 mg/kg/dose every 6 hours, and ranitidine, 2 mg/kg/dose every 8 hours, with saline placebo.
Outcomes	Gastro-oesophageal reflux features	Apnoea episodes, Gastroesophageal episodes	Vomiting, Neurobehavioural, Back Arching, Gagging, Irritability/crying/fussing, Bradycardia, Oxygen Desaturation, Apnoea	Oesophageal pH, Gastric pH, Vomiting, Apnoea, Bradycardia, Choking, Behavioural changes, Blood biochemistry, Blood picture	Crying, Regurgitation, Stop feeding, Refuse feed, Arching back, Wheezing, Coughing, Hoarseness, Adverse Events	Bradycardia episodes per day.

Risks of Bias assessments of trials are summarized in Figure 2 and supplementary Appendix 3. The evaluations of the level of evidence of outcomes according to the GRADE approach are summarized in supplementary Appendix 4.

A total of 302 participants were enrolled in the 6 included trials, of which, 4 studies included only preterm infants. Omari et al[10] included preterm infants between 34 and 40 weeks gestational age, Corvaglia (a) et al[11] and Corvaglia (b) et al [12] included ≤33 weeks gestational age and Wheatley et al [9] included those with a gestational age of <37 weeks at birth and a corrected gestational age at enrolment of <44 weeks. Orenstein et al[13] and Davidson et al[14] included both preterm infants and full-term infants.

Primary Outcome: All 6 studies assessed various reflux symptoms (See Appendix 5 in supplement). The inclusion criteria for each study defined GORD differently. Omari et al, Corvaglia (a) et al and Orenstein et al included infants with symptomatic GORD. Omari et al also required 24-hour pH monitoring. Davidson et al included those with more than one of the following: apnoea, vomiting or gagging and irritability or pain. Wheatley et al required a clinical diagnosis of GORD and bradycardia attributed to GOR, as well as 2 episodes of bradycardia per day and Corvaglia (a) et al specifically required subjects to have recurrent postprandial apnoeas.

None of the studies reported on the prespecified secondary outcomes, namely: time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis and suspected or proven sepsis. Orenstein et al looked at treatment-emergent adverse events and serious adverse events including upper respiratory tract infections, constipation, dermatitis, ear infections, fever, lower respiratory tract infection, respiratory tract congestion, rhinorrhoea, candidiasis, diarrhoea (excluding infective), vomiting, alkaline phosphatase increase, and others.

Effects of Interventions

Sodium Alginate (Gaviscon) vs Placebo

There was significant decrease in total GORs, pH-GORs, aMII-GORs, RIpH and Proximal GORs. [11, 12] (Table 2)

Table 2. Effect of Alginates (Gaviscon) use in preterm infants

Studies	Antacids	Control	P
Corvaglia (a) et al			
Total GORs	49.00 (28.50–67.00)	58.50 (33.50–75.75)	0.024
Liquid GORs	21.50 (12.25–32.00)	21.50 (13.50–39.75)	0.432
Gaseous GORs	2.00 (0.25–7.50)	3.00 (0.00–14.75)	0.040
Mixed GORs	3.00 (2.00–5.75)	3.00 (1.00–5.00)	0.614
pH-GORs	17.00 (6.00–29.75	29.00 (13.50–44.50)	0.002
aMII-GORs	4.00 (2.00–8.25)	6.00 (2.25–11.75)	0.050
NaMII-GORs	19.00 (10.00–32.75)	18.50 (8.50–33.75)	0.743
RIpH	4.0 (1.8–13.1)	7.6 (3.3–17.0)	0.030
aMII-GOR-BEI	0.2 (0.1–0.6)	0.4 (0.1–1.0)	0.036
NaMII-GOR-BEI	1.2 (0.5–1.9)	0.9 (0.5–1.7)	0.822
Distal GORs (no.)	18.00 (11.25–27.00	15.00 (9.25–26.00)	0.959
Proximal GORs (no.)	5.50 (4.00–9.00)	7.50 (3.00–12.00)	0.030
Corvaglia (b) et al			
Total GOR episodes	9 (0–33)	20.5 (1–42)	0.001
pH-GOR	2 (0–26)	7.5 (0–23)	0.004
a-MII-GOR	1 (0–5)	3 (0–16)	0.001
Na-MII-GOR	4.5 (0–22)	6 (1–21)	0.145
RIpH	0.9 (0–23.2)	8.4 (0–44.2)	0.001
a-MII-BEI	0.17 (0–2)	0.5 (0–8.1)	0.002
Na-MII-BEI	0.75 (0–5.7)	1.0 (0.1-9.2)	0.982

GOR: Gastro-Oesophageal Reflux;MII: multichannel intraluminal impedance monitoring; pH-GOR: GOR episodes detected only by pH monitoring; aMII-GOR: acid GOR episode detected by MII; NaMII-GOR: non-acid GOR episode detected by MII; RIpH: Reflux Index detected only by pH monitoring; aMII-GOR-BEI: acid MII-GOR-bolus exposure index; NaMII-GOR-BEI: non-acid MII-GOR-bolus exposure index

Esomeprazole vs Placebo

No significant results were obtained from this study which was discontinued prematurely due to poor enrolment. [14](Table 3)

Table 3. Effect of Proton Pump Inhibitors use in preterm infants

Studies	Antacids	Control	P
Esomeprazole vs Placebo			
Davidson et al			
Total number of GORD-related signs and symptoms (percentage of change from baseline after 14 days of treatment)	-14.7%	14.1%	0.92
Gastrointestinal events	-8.39%	10.16%	0.42
Neurobehavioral events	-3.54%	-3.98%	0.94
Cardiorespiratory events	-38.94%	-41.17%	0.89
Omeprazole vs Placebo			
Omari et al			
Gastric acidity (%time pH<4)	13.9 ± 5.1	53.8 ± 6.8	<0.0005
Oesophageal acid exposure (%time pH<4)	4.9 ± 3.4	19.0 ± 4.5	<0.01
No. of acid GOR episodes	119.4 ± 20.	59.6 ± 26.7	<0.05
No. of oesophageal acid GOR >5min	8.0 ± 2.1	3.0 ± 2.0	<0.01
Lansoprazole vs Placebo			
Orenstein et al			
Primary efficacy: Responder rate, n (%)	44 (54%)	44 (54%)	NS
AEs	50 (62%)	37 (46%)	NS
SAEs	10 (12%)	2 (2%)	0 .032

GORD: Gastro-Oesophageal Reflux disease; GOR: Gastro-Oesophageal Reflux; NS, not significant; AEs: adverse events; SAEs: serious adverse events.

Omeprazole vs Placebo

Analyses on the basis of pH recordings showed that Omeprazole therapy significantly reduced the oesophageal acid exposure % time pH<4 (omeprazole vs placebo, mean ± standard error mean, 4.9 ± 3.4 vs 19.0 ± 4.5, paired t-test P<0.01) and reduced gastric acidity % time pH<4 (13.9 ± 5.1 vs 53.8 ± 6.8, P<0.0005). [10](Table 3)

There were no significant changes to symptom frequency (vomiting, apnoea, bradycardia, choking, behavioural changes) or blood results.

Lansoprazole vs Placebo

No significant results were obtained from this trial, 54% of infants in both double-blind groups responded to intervention. [13] (Table 3)

Metoclopramide and Ranitidine vs Placebo

18 patients were enrolled, and 17 completed the study, with a gestational age of 29 ± 3 weeks. There was a significant decrease in the number of bradycardia episodes per day in the mean combined placebo time periods compared to the mean combined drug time periods [3.6 (SD 2.7) vs 4.6 (SD 3.1)), P = 0.04], and in bradycardia episodes over time (P<0.001), with fewer episodes during placebo periods. [9]

DISCUSSION

This systematic review demonstrates the lack of efficacy and safety data for anti-GORD drug therapy in preterm infants. The heterogeneity of the interventions precluded a meta-analysis.

Alginates

Corvaglia (a) and (b) et al. found that sodium alginate significantly decreased the number of acid gastro-oesophageal reflux detected either by pH and impedance monitoring, and also acid oesophageal exposure, without any influence on non-acid gastro-oesophageal reflux.

However, sodium alginate didn't reduce the total number of apnoea of prematurity nor GOR-related apnoeas.[12]

Furthermore, sodium alginate was found to lower the number of GORs reaching the proximal oesophagus and also the number of gaseous GORs. Corvaglia (a) et al reports that participants were observed over a 24 hour period, and data was collected after 8 meals, whereas in Corvaglia (b) participants were observed over 9 hours, and data was collected after 2 meals. It is possible that the authors of Corvaglia (b) et al chose only to report data from the 9 hour period, instead of using the full 24 hour data, in order to report more significant results. This discrepancy diminishes the validity of the papers and suggests that the evidence should not be applied to clinical practice.

Proton pump inhibitors

Omari et al. showed that 0.7 mg/kg omeprazole given once daily was effective in reducing the frequency of acid reflux episodes and the overall degree of oesophageal acid exposure in premature infants. The drug-dosing regimen used appeared safe based on adverse event reporting and blood screening. However, due to the small number of participants enrolled in the study (n=10), it would be difficult to state whether this evidence is applicable in everyday practice and more trials must be carried out into the effectiveness of omeprazole.

There were no significant differences in the number of GORD-related signs and symptoms between neonates receiving esomeprazole or lansoprazole vs placebo.[13, 14]

Serious AEs, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo group (10 vs 2; P= .032); There was a 35% loss of follow up for participants receiving lansoprazole and 36% for participants receiving placebo. It is unclear whether this caused a significant imbalance in characteristics between the two interventions. Therefore, applicability into everyday practice is low because loss to follow-up can severely compromise validity as those lost to follow-up could have a different prognosis than those who

complete the study. The number of AEs was similar between neonates receiving esomeprazole vs placebo.

H2-receptor antagonists

A retrospective cohort study conducted by Romainea et al. [15] in USA concluded that H2 blocker use was associated with increased risk of the combined outcome of death, NEC, or sepsis in hospitalized VLBW infants. Another recent retrospective cohort study showed that ranitidine use was associated with an increased risk of infections and mortality in preterm infants, but not with NEC.[16]

Wheatley showed that ranitidine did not reduce, and may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GOR. Wheatley compared the combination of 2 interventions together against a placebo, ranitidine, a H2 receptor antagonist and metoclopramide, a dopamine receptor antagonist. With regards to applicability, the data derived from this study actually suggests that combining ranitidine and metoclopramide may be detrimental to patients and should therefore be avoided in clinical practice, as it showed a significant increase in bradycardia episodes during drug periods. This may be caused by significant interactions between the 2 drugs that could either decrease the efficacy of either or both of drugs or perhaps cause adverse effects. Leucuta et al, found pharmacokinetic changes, such as an increased half-life, in metoclopramide, when taken with ranitidine.[17] However, it is quite likely that this is a chance finding, given the small number of participants enrolled in the study (n=18). Previous studies into the combined effectiveness of ranitidine and metoclopramide suggest that this treatment is effective at increasing gastric pH and reducing the side effects of GORD, and do not mention any significant drug induced side effects or drug interactions.[18,19]

Summary of main results

Omeprazole was successful in reducing gastric and oesophageal pH, but not the symptoms associated with GORD, which may imply that omeprazole had little effect on non-acid GOR episodes. The combined use of ranitidine and metoclopramide actually proved counter-effective,

with placebo periods giving significantly less bradycardia episodes than drug periods. Sodium alginate significantly reduced GOR episodes, though had no effect on the reduction of apnoeas. Esomeprazole and Lansoprazole appeared to have no significant effect on symptoms of GORD.

Limitations

Not all studies met the inclusion criteria outlined in the methods. We initially stated that only preterm infants <37 weeks gestation were to be included in this review, however both Davidson et al and Orenstein et al included data for full-term infants as well as preterm, some of whom were >37 weeks gestation. Authors were contacted to obtain exclusively preterm data, however, replies were not received. We included these studies in this review due to the high percentage of preterm infants enrolled in the trials. The methods stated that the only interventions that were to be considered were H2 receptor antagonists, proton pump inhibitors and alginates, however Wheatley et al assessed the combined effects of both metoclopramide (dopamine receptor antagonist) and ranitidine (H2 receptor antagonist). We still decided to report this outcome as the inclusion of the H2 receptor antagonist as it is of interest to the reader in general who must bear in mind this was a combined intervention.

Agreements or disagreements with other studies or reviews

To our knowledge, this review is the first to look into the effects of antacids in preterm infants. Terrin et al. in a retrospective study of 274 very low birth weight infants reported that the risk of necrotizing enterocolitis, nosocomial infection and mortality were significantly higher in the infants exposed to ranitidine.[4] However, non-prospective, non-controlled and un-blinded design features limited its significance. A Cochrane review by Tighe et al looking at the effects of pharmacological treatment for the management of GORD in children concluded that although there is evidence to support pharmacological use in older children, use in infants is unsupported due to lack of robust RCT evidence.[20]

Cohen et al. in a recent review suggested that the use of GORD medications should only be used after non-pharmacological measures have been taken with incomplete success as acid

suppression may place immune-deficient infants and children at risk for the development of lower respiratory tract infections and nosocomial sepsis. [21]

Author's Conclusions

There is insufficient evidence on the efficacy and safety of antacids in preterm infants. The lack of research in this area of medicine is a problem that must be addressed in this population of patients. Adequately powered, randomised, controlled trials in preterm infants are needed to determine the safety and effectiveness of these commonly used medications.

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Study concept and design: Dr. Dorling and Dr. Schoonakker conceived and designed the study.

Acquisition of data: Dr. Mackie and Dr. Dermyshi.

Analysis and interpretation of data: Dr. Dermyshi, Dr. Mackie, Dr. Kigozi, Dr Schoonakker and Dr. Dorling.

Drafting of the manuscript: Dr. Dermyshi, Dr. Kigozi, Dr. Dorling.

Critical revision of the manuscript for important intellectual content: Dr. Dorling

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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References

1. Corvaglia L, Monari C, Martini S, et al. Pharmacological therapy of gastroesophageal reflux in preterm infants. *Gastroenterol Res Pract*. 2013; 2013:714564. doi: 10.1155/2013/714564.

2. Rossor T, Andradi G, Bhat R Greenough A. Investigations and management of gastro-oesophageal reflux in United Kingdom neonatal intensive care units Acta Paediatrica 2018 January; DOI:10.1111/apa.14073.

3. Guillet R, Stoll BJ, Cotten CM, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; 117(2):e137-42.

4. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012 Jan;129(1):e40-5. doi: 10.1542/peds.2011-0796.

5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009 Oct; 62(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006.

6. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (updated March 2011). *The Cochrane Collaboration* 2011 (Available at: www.cochrane-handbook.org.).

7. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011 Oct 18; 343:d5928. doi: 10.1136/bmj.d5928.

8. Guyatt G, Oxman AD, Akl EA, et al: GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011 Apr; 64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026.

9. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr*. 2009 Oct; 155(4):516-21. doi: 10.1016/j.jpeds.2009.03.044.

10. Omari TI, Haslam RR, Lundborg P, et al. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. *Journal of pediatric gastroenterology and nutrition* 2007; 44(1):41-4.

11. (a) Corvaglia L, Aceti A, Mariani E, et al. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants. *Aliment Pharmacol Ther.* 2011 Feb; 33(4):466-70. doi: 10.1111/j.1365-2036.2010.04545.x.

12. (b) Corvaglia L, Spizzichino M, Zama D, et al. Sodium Alginate (Gaviscon(R)) does not reduce apnoeas related to gastro-oesophageal reflux in preterm infants. *Early Hum Dev.* 2011 Dec; 87(12):775-8. doi: 10.1016/j.earlhumdev.2011.05.013.

13. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr.* 2009 Apr; 154(4):514-520.e4. doi: 10.1016/j.jpeds.2008.09.054.

14. Davidson G, Wenzl TG, Thomson M, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *J Pediatr.* 2013 Sep; 163(3):692-8.e1-2. doi: 10.1016/j.jpeds.2013.05.007.

15. Romainea A, Ye D, Ao Z, et al. Safety of Histamine-2 Receptor Blockers in Hospitalized VLBW Infants. *Early Hum Dev.* 2016 Aug; 99:27-30. doi: 10.1016/j.earlhumdev.2016.05.010.

16. Santana RNS, Santos VS, Ribeiro-Júnior RF, et al. Use of ranitidine is associated with infections in newborns hospitalized in a neonatal intensive care unit: a cohort study. *BMC Infect Dis.* 2017 May 30; 17(1):375. doi: 10.1186/s12879-017-2482-x.

17. Leucuţa A, Vlase L, Farcău D, et al. Pharmacokinetic interaction study between ranitidine and metoclopramide. *Romanian journal of gastroenterology* 2004; 13(3):211-4.

18. Hong J-Y. Effects of Metoclopramide and Ranitidine on Preoperative Gastric Contents in Day-Case Surgery. *Yonsei Medical Journal* 2006; 47(3):315-318. doi:10.3349/ymj.2006.47.3.315.

19. Bala I, Prasad K, Bhukal I, Nakra D, Pratap M. Effect of preoperative oral erythromycin, erythromycin-ranitidine, and ranitidine-metoclopramide on gastric fluid pH and volume. *J Clin Anesth.* 2008 Feb; 20(1):30-4. doi: 10.1016/j.jclinane.2007.08.002.

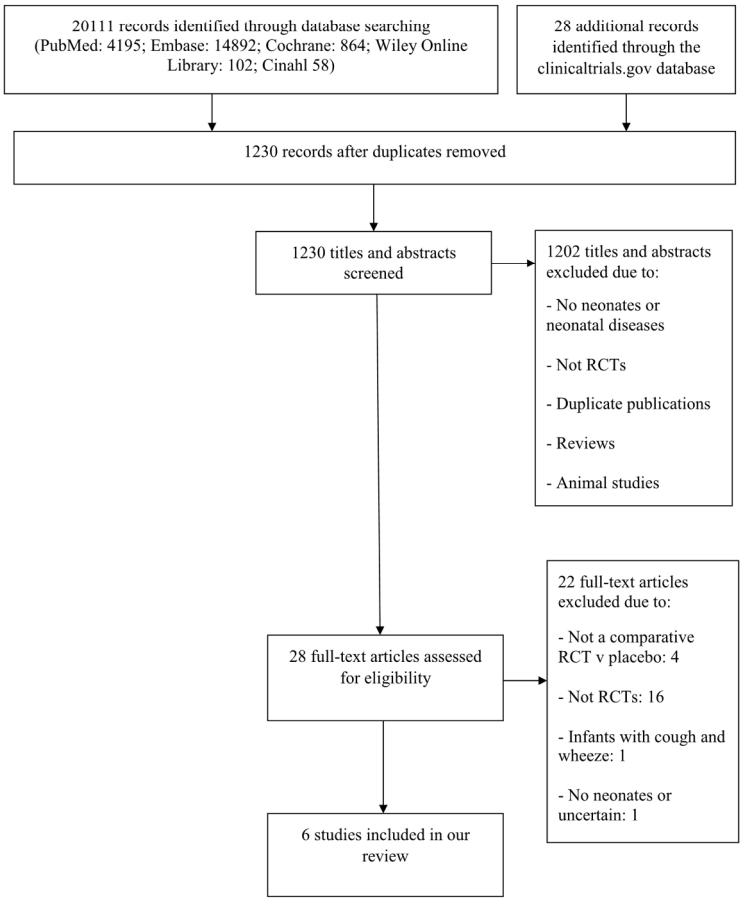
20. Tighe M, Afzal NA, Bevan A, et al. *Cochrane Database Syst Rev*. 2014 Nov 24; (11):CD008550. doi: 10.1002/14651858.CD008550.pub2.

21. Cohen S, Bueno de Mesquita M, Mimouni FB. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. *Br J Clin Pharmacol.* 2015 Aug; 80(2):200-8. doi: 10.1111/bcp.12619.

Tables

Figures

Figure 1: Study flow diagram



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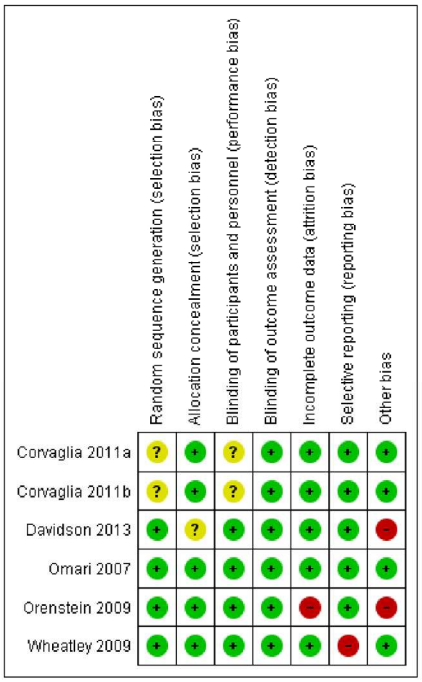

Figure 2- Risk of Bias Summary

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Appendix 1 Search strategies

Search Methods for Identification of Studies

The standard search of the Cochrane Neonatal Review Group, including electronic searches of the Cochrane central register of controlled trials (CENTRAL, The Cochrane Library), MEDLINE (1966 – to present), EMBASE (1980- to present) and CINAHL (1982 –to present) was used. There was no language restriction applied.
The following search terms were applied for each database:

MEDLINE (via PubMed) was searched using the following search strategy:

#1	(infant) OR infants	(infant) OR infants
#2	(neonate) OR neonates	(neonate) OR neonates
#3	(preterm) OR preterms	(preterm) OR preterms
#4	(preterm) AND (neonate OR neonates OR infants)	(preterm) AND (neonate OR neonates OR infants)
#5	(gastroesophageal reflux) AND infants	(gastroesophageal reflux) AND infants
#6	(gastroesophageal) AND reflux	(gastroesophageal) AND reflux
#7	(((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants))	(#6) AND (#4)
#8	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) NOT animals	(#7 NOT animals
#9	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND (therapy OR therapeutic OR therapeutics)	(#7) AND (therapy OR therapeutic OR therapeutics)
#10	(((((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND (therapy OR therapeutic OR therapeutics))) NOT animals	(#9 NOT animals
#11	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND alginates	(#7) AND alginates
#12	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND rabeprazole	(#7) AND rabeprazole
#13	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND pantoprazole	(#7) AND pantoprazole

#14	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND omeprazole	(#7) AND omeprazole
#15	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND proton pump inhibitors	(#7) AND proton pump inhibitors
#16	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND esomeprazole	(#7) AND esomeprazole
#17	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND ranitidine	(#7) AND ranitidine
#18	((((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND histamine h2 receptors) AND antagonist	(#7) AND (histamine h2 receptors) AND antagonist
#19	((((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND histamine h2 receptors) AND antagonist Schema: all	(#7) AND (histamine h2 receptors) AND antagonist) Schema: all
#20	(Controlled clinical trial[tw] OR Clinical Trial[tw] OR Clinical trial [ptyp] OR Controlled)	(Controlled clinical trial OR Clinical Trial OR Clinical trial OR Controlled)
#21	(Randomized Controlled Trial[tw] OR Randomized Controlled Trial[ptyp] OR random* [tw])	(Randomized Controlled Trial OR Randomized Controlled Trial OR random)
#22	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND ((Randomized Controlled Trial[tw] OR Randomized Controlled Trial[ptyp] OR random* [tw]))	(#7) AND (#21)

EMBASE was searched using the following search strategy:

1.	prematurity/ or preterm.mp.
2.	newborn/
3.	infant/
4.	gastroesophageal reflux.mp. or gastroesophageal reflux/

5.	reflux.mp.
6.	antacid.mp. or antacid agent/
7.	clinical trial/
8.	proton pump inhibitors.mp. or proton pump inhibitor/
9.	histamine H2 receptor antagonist/
10.	alginate.mp. or alginic acid/
11.	1 and 4
12.	6 and 11
13.	1 and 6
14.	7 and 11
15.	8 and 11
16.	9 and 11
17.	10 and 11
18.	12 or 14 or 15 or 16 or 17
19.	7 and 18
20.	random.mp.
21.	19 and 20

COCHRANE Library (CENTRAL and Cochrane Database of Systematic Reviews) were searched using the following search strategy:

#1	preterm
#2	prematurity
#3	neonate or neonates

#4	newborn
#5	infant or infants
#6	gastroesophageal reflux
#7	reflux
#8	antacid
#9	proton pump inhibitors
#10	H2 antagonist
#11	alginate
#12	clinical trials
#13	randomised
#14	#1 or #2 or #3 or #4 or #5 and #6
#15	#14 and #8
#16	#15 and #12
#17	#16 and #13

Cinahl: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial) AND (gastroesophageal reflux OR reflux) AND antacid)

Appendix 2

Characteristics of Excluded Studies

Excluded Study	Reason for Exclusion
Abdel-Rahman 2004	Not a RCT; uses different doses of Nizatidine
Adamko 2012	Exclude as infants with cough and wheeze.
Atasay 2010	Not a RCT.
Cresi 2006	Not a RCT
Dhillon 2004	Not a RCT
Golski 2010	Not a RCT
Kierkus 2011	Not a RCT, compared 2 different doses of Pantoprazole
Le 1992	Not a RCT, compared 2 different doses of Alginate
Loots 2014	States that patients have been 'referred' so assumed that these are GP patients and not preterm infants.
Omari 2009	Not a RCT.
Orenstein 2005	Comparison of 2 doses of Nizatidine
Sandstrom 2012	Not a comparative RCT v placebo (different doses of esomeprazole)
Springer 2008	Not a RCT.
Sutphen 1986	Not a RCT
Tammara 2011	Compared 2 doses of pantoprazole, did not use placebo.
Ward 2010	Compares 2 doses of pantoprazole
Weldon 1972	Not a RCT
Wenning 2005	Not a RCT
Zhang 2008	Not a RCT
Slaughter 2016	Not RCT
Santana 2017	Not RCT
Romaine 2016	Not RCT

Appendix 3

Risk of bias in included studies

When assessing the quality of RCTs, bias is a very important consideration. We have looked at the various areas where bias may arise throughout the trials and given this an overall level of risk.

Selection

Allocation was randomised with Davidson et al using block randomisation, and with Omari et al, Orenstein et al and Wheatley et al using a random number generator. Corvaglia (b) et al and Corvaglia (a) et al did not report any form of random sequence generation for allocation. With regards to allocation concealment, Davidson et al is unclear about its methods of concealment.

Performance

Davidson et al, Omari et al, Orenstein et al and Wheatley et al all state or imply that their placebo was prepared and appeared similar to the drug, thus ensuring the blinding of participants and personnel. Corvaglia (b) et al and Corvaglia (a) et al were not clear about their methods taken to ensure blinding.

Detection

Data were assessed by independent assessors for Corvaglia (b) et al, Corvaglia (a) et al, Davidson et al and Wheatley et al minimising risk of detection bias. No apparent detection bias was found in Omari et al and Orenstein et al.

Attrition

Corvaglia (a) et al, Corvaglia (b) et al and Omari et al reported all outcomes. Davidson et al and Wheatley et al both lost 1 participant each to follow-up during the study; Davidson et al was due to efficacy data not being available, Wheatley et al does not give an explanation. 57 of 162 participants in Orenstein et al discontinued the treatment early giving a high risk of attrition bias. 55 of these participants went on to take open-label lansoprazole, the results of which were reported and incomplete data was carried forward to the 4th week for the double-blind results. It is unclear what happened to the remaining 2 participants.

Risk of Bias Table – Corvaglia (b) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear Risk	The DG ('drug-given') meal was randomly chosen in order to avoid any possible carry-over effect. As same study as Corvaglia (a) et al, it seems this was a random choice of data from 2 DG ('drug-given') and DF ('drug-free') feed in a 9 hour window.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	The investigator was blind to the administration of sodium alginate. pH-MII and PSG data were analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

Risk of Bias Table - Corvaglia (a) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear Risk	Each patient assessed over 24 hour period; 8 feeds with 2nd, 4th, 6th and 8th feed was DG ('drug-given') meal. No randomisation used.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	During layout analysis the investigator was blind to the administration of sodium alginate. pH-MII and PSG data were then analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

Risk of Bias Table – Davidson et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A block randomisation scheme was used, stratified by centre.
Allocation concealment (selection bias)	Unclear Risk	Method of randomisation allocation not clearly described.
Blinding of participants and personnel (performance bias)	Low Risk	Treatments blind to all, method described but not explicit that the active and placebo preparations looked identical.
Blinding of outcome assessment (detection bias)	Low Risk	Two blinded central readers independently reviewed the videos and cardiorespiratory data.
Incomplete outcome data (attrition bias)	Low Risk	One patient in the placebo group completed the study, but was lost to follow-up between study completion and the safety follow-up visit.
Selective reporting (reporting bias)	Low Risk	One patient in the esomeprazole group was excluded from the modified ITT analysis because of invalid efficacy measurements.
Other bias	High Risk	Sponsored by AstraZeneca LP (Wilmington, Delaware). AstraZeneca was involved in the design and conduct of the study; collection, analysis, and interpretation of the data; and the preparation, review, and approval of the trial report manuscript. 2 authors, both funded by AstraZeneca developed the first draft of the trial report manuscript. 3 employees of AstraZeneca, included work on this manuscript among their job responsibilities and also had limited AstraZeneca stock ownership. 3 authors had received grants and research support from AstraZeneca.

Risk of Bias Table – Omari et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A stock solution containing either 5mg/mL omeprazole or sterile water was prepared and dispensed by pharmacy according to a randomisation schedule determined using a random number generator.
Allocation concealment (selection bias)	Low Risk	Drug or placebo prepared and dispensed using random number generator.
Blinding of participants and personnel (performance bias)	Low Risk	A stock solution was prepared which contained either omeprazole or sterile water (placebo). It is not clear how similar these were.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent detection possible.
Incomplete outcome data (attrition bias)	Low Risk	Follow up data complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	AstraZeneca R&D Molndal assisted by performing plasma omeprazole assays.

Risk of Bias Table – Orenstein et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Double-blind treatment assignments were made through a central web-based system according to a schedule that was computer generated.
Allocation concealment (selection bias)	Low Risk	States that treatment assignments were concealed to study personnel
Blinding of participants and personnel (performance bias)	Low Risk	Appearance, reconstitution, and administration of lansoprazole and placebo were identical.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent bias in outcome assessment.
Incomplete outcome data (attrition bias)	High Risk	55 of 162 discontinued treatment early for open label treatment. For such subjects, the last week of available data was carried forward to 4th week for the individual symptoms and global severity assessments.
Selective reporting (reporting bias)	Low Risk	All randomised infants administered 1 or more dose(s) of study drug were included in the intention-to-treat data set for efficacy and safety analyses.
Other bias	High Risk	Takeda Global Research & Development Center, Inc sponsored the clinical trial, employed 2 authors and data interpretation and analysis was also undertaken by their employees.

Risk of Bias Table – Wheatley et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Study group assignment (order of medication and placebo administration) was determined by blocked random number generation.
Allocation concealment (selection bias)	Low Risk	A research pharmacist assigned the study group for each patient at the time of enrolment.
Blinding of participants and personnel (performance bias)	Low Risk	Investigators, clinicians, and parents were all blind to the group assignment during the study period. Intravenous preparations were used because they were clear and colourless. Saline placebos of the same volume and colour were administered during the placebo periods.
Blinding of outcome assessment (detection bias)	Low Risk	At the end of the study period for each infant, after the study outcome data were summarised for the infant, the investigator contacted the pharmacist to ascertain the group assignment (order of medication and placebo administration) for the infant, eliminating bias as data were analysed prior to finding out group assignment.
Incomplete outcome data (attrition bias)	Low Risk	One infant was enrolled in the study but was then withdrawn, with no explanation for the withdrawal.
Selective reporting (reporting bias)	High Risk	Clinicaltrials.gov record shows that the authors originally planned to analyse and present data on apnoea also. This was not included and the protocol was changed on clinicaltrials.gov.
Other bias	Low Risk	No conflicts of interest or sponsorship.

Appendix 3

sTable 1- Summary of findings: Sodium alginate in preterm infants

Sodium alginate compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: Sodium alginate **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes assessed with: Combined pH and impedance monitoring (follow-up: range 6h to 24h)	In two studies Sodium alginate significantly decreased the number of acid GOR episodes but did not influence the number of non-acid GOR episodes. In one study Total GOR Episodes: RR 0.59 (0.53 to 0.65) (95% CI). In the other study, sodium alginate significantly decreased the number of GOR (DG vs. DF: median 49 vs. 58.5) [a,b,c]	60 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]
A reduction in reflux symptoms (apnoea related to GOR) assessed with: Combined multichannel intraluminal impedance and pH monitoring and polysomnography (follow-up: 6h)	The frequency of apnoeas related to GOR did not differ between DG and DF meals (median [range] 0 [0–0.67] vs. 0 [0–0.47]). Total Apnoea Episodes: RR 1.06 (0.96 to 1.18) (95% CI) [a,b]	28 (1 RCT)	⨁⨁◯◯ LOW [d,e]
Adverse events assessed with: Not specified (follow-up: range 6h to 24h)	No adverse event was recorded during the study period.	60 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	None of the included studies examined the effect of sodium alginates on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. DG: drug given

b. DF: drug free

c. GOR: gastroesophageal reflux

d. Evidence downgraded by 1 point (-1) for risk of selection bias.

e. Evidence downgraded by 1 point (-1) for indirectness as only a single study contributed data, and evidence was therefore based on a single patient population.

sTable 2 - Summary of findings: Proton pump inhibitors in preterm infants

Proton pump inhibitors compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: Proton pump inhibitors **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes assessed with: Twenty-four-hour esophageal pH monitoring (reflux index score)	Omeprazole therapy (10 participants; 1 study) significantly reduced gastric acidity, oesophageal acid exposure and the number and duration of acid reflux episodes compared to placebo. There was no statistically significant difference between the esomeprazole and placebo groups in the percentage of change from baseline after 14 days of treatment in the total number of GORD-related signs and symptoms (52 participants; 1 study).	62 (2 RCTs)	⨁⨁◯◯ LOW [a,b]
A reduction in reflux symptoms assessed with: Bedside symptom charts (vomit/regurgitations, choking/coughing, bradycardia attributed to GOR, behavioural/crying, feeding difficulties, irritability or pain, recurrent postprandial apnoeas and oxygen desaturation within two hours postprandial period)	Despite the normalization of acid reflux in most patients, the number of symptomatic events of vomiting, apnea, bradycardia or behavioral changes was not significantly changed by omeprazole (10 participants; 1 study). One study (162 participants) detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GORD. No significant differences were observed between the esomeprazole and placebo groups (52 participants; 1 study) in the percentage of change from baseline to the end of treatment in the total number of gastrointestinal, neurobehavioral or cardiorespiratory events.	224 (3 RCTs)	⨁⨁◯◯ LOW [a,b,c]
Adverse events	Treatment-emergent serious AEs (SAEs), particularly lower respiratory tract infections, were significantly more frequent in the lansoprazole group compared with the placebo group (10 vs 2; P.032). Overall, few adverse events (AEs) were reported, and the number of patients with AEs was similar between the esomeprazole and placebo groups. The most commonly reported AE was decrease in oxygen saturation (52 participants; 1 study). No SAEs were reported in the esomeprazole-treated patients and 4 SAEs (neonatal bradycardia, cyanosis, inappropriate device signal detection, and infantile apneic attack) were reported in 3 placebo patients. Omeprazole therapy (10 participants; 1 study) was not associated with the occurrence of any serious adverse events.	224 (3 RCTs)	⨁⨁◯◯ LOW [a,b,c]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	None of the included studies examined the effect of proton pump inhibitors on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(0 studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

sTable 3 - Summary of findings: H2 receptor antagonists in preterm infants

H2 receptor antagonists compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: H2 receptor antagonists **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes	The included study did not examined the effect of H2 receptor antagonists on the reduction of reflux episodes.	(0 studies)	-
A reduction in reflux symptoms (Bradycardia) assessed with: Telemetry and nursing documentation	No evidence of efficacy was found for Ranitidine to reduce bradycardia. The mean number of bradycardia episodes per day in the combined drug periods was 4.6 (SD = 3.1), and the mean number of episodes per day in the combined placebo periods was 3.6 (SD = 2.7) There was a statistically significant difference, with fewer episodes during the placebo periods. The mean difference (drug minus placebo) was 0.94 episodes per day, with a P value of 0.04.	17 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Adverse events assessed with: Clinical assessment	There were no adverse effects attributed to ranitidine. However, it may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GOR.	17 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	No studies examined the effect of H2 receptor antagonists on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(0 studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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A Systematic Review

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Antacid therapy for gastroesophageal reflux in preterm infants:

A Systematic Review

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PROSPERO registration number: CRD42017078778 (www.crd.york.ac.uk/PROSPERO; ref CRD42017078778).

Abbreviations:

H2 Ras: Histamine-2 receptor antagonists;

PPI: Proton Pump Inhibitors;

GORD: Gastro-Oesophageal Reflux disease;

GOR: Gastro-Oesophageal Reflux;

AEs: adverse events;

SAEs: serious adverse events;

NEC: Necrotising enterocolitis;

RCTs: Randomized controlled trials;

DG: Drug-given;

DF: Drug-free;

MII: multichannel intraluminal impedance monitoring;

pH-GOR: GOR episodes detected only by pH monitoring;

aMII-GOR: acid GOR episode detected by MII;

NaMII-GOR: non-acid GOR episode detected by MII;

RIpH: Reflux Index detected only by pH monitoring;

aMII-GOR-BEI: acid MII-GOR-bolus exposure index;

NaMII-GOR-BEI: non-acid MII-GOR-bolus exposure index.

Abstract

Background

Gastroesophageal reflux is prevalent in preterm infants. Despite widespread use in clinical practice, there is still much controversy over the efficacy and safety of drug interventions, particularly antacid therapy.

Objective

To systematically review the effects of antacid therapy on preterm infants with symptoms of gastroesophageal reflux, and to assess the safety of these interventions.

Methods

We carried out an electronic search of the Cochrane central register of controlled trials (CENTRAL, The Cochrane Library), MEDLINE (1966 – to present), EMBASE (1980- to present) and CINAHL (1982 –to present) as well as other online sources. Participants were preterm infants (<37 weeks gestation) with gastroesophageal reflux disease who were receiving care on a neonatal unit. We assessed the effects of H2 receptor antagonists, proton pump inhibitors and alginates against placebo, primarily to see if they reduced the symptoms of reflux.

Results

6 studies were included in this review. Meta-analysis could not be carried out due to a lack of studies assessing the same intervention with the same outcomes. Omeprazole therapy significantly reduced the oesophageal acid exposure percentage time with pH<4 ($p<0.01$) and sodium alginate significantly decreased gastroesophageal reflux episodes ($p=0.024$). Metoclopramide and ranitidine showed a significant increase in gastroesophageal reflux disease symptoms versus placebo ($p<0.04$). No significant results were found for the use of esomeprazole or lansoprazole versus placebo.

Conclusions

There is insufficient evidence available to conclude whether antacid therapy is effective or safe when treating gastroesophageal reflux disease in preterm infants. Further research is needed into this topic and caution should be taken when administering antacids to preterm infants.

Systematic review registration number: CRD42017078778

Keywords: systematic review; gastroesophageal reflux disease; oesophageal reflux; antacids; histamine receptor antagonists; proton pump inhibitors; alginate; preterm; infant; low birth weight.

What is known?

- Gastroesophageal reflux is a prominent condition among preterm infants.
- Antacids are often used to treat GORD, despite the lack of good quality evidence to support its use.
- Studies have shown a significant positive correlation between the use of H2 RAs and important complications.

What is new?

- There is limited evidence supporting the use of antacids in preterm infants
- Omeprazole reduced gastric and oesophageal pH, but did not alter GORD symptoms. Esomeprazole and Lansoprazole had no significant effect on GORD signs and symptoms.
- Combined use of ranitidine and metoclopramide appears counter-effective, with placebo periods giving less bradycardia episodes versus drug periods.

Background

Gastroesophageal reflux (GOR) is a prominent condition among preterm infants. Symptoms such as apnoeas, desaturation, bradycardia, vomiting, poor weight gain and irritability have been attributable to GOR, which is called gastroesophageal reflux disease (GORD), when symptoms are severe. GORD has been reported to cause irritability, frequent vomiting, apnoea and bradycardia, aspiration pneumonia, aversion to feeding and exacerbation of chronic lung disease in term and preterm infants with associated resource implications from longer hospital stays. Despite this, controversy remains over how it should be treated. Currently, non-pharmacologic therapies are generally the first line of treatment in GORD with pharmacological therapies reserved for those who do not respond.[1] Antacids containing alginate, Histamine-2 receptor antagonists (H2 RAs) and proton pump inhibitors (PPI) are among the most common interventions used with 60%, 53% and 23% of UK neonatal units using these products respectively. [2]

Studies have also shown a significant correlation between the use of H2RAs and important complications. [3, 4] Guillet et al showed H2-blocker use was associated with an increased incidence of necrotising enterocolitis (NEC) (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.34–2.19; P < .0001). [3]

There continues to be a widespread use of antacid therapy in neonatal units today despite the evidence gaps. This review was carried out to systematically evaluate the evidence of efficacy and safety of antacid treatment for GORD in preterm infants and to highlight potential areas for future research.

Objectives

Primary objective:

To assess the efficacy of antacid therapy in preterm infants diagnosed with gastroesophageal reflux disease.

Secondary objective:

To assess the safety of antacid therapy in preterm infants diagnosed with gastroesophageal reflux disease.

Material and methods

We used Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Cochrane Handbook of Systematic Reviews of Interventions approach for conducting and reporting systematic reviews and meta-analyses of randomized controlled trials (RCTs).[5,6] The methodology of this systematic review was published in PROSPERO (www.crd.york.ac.uk/PROSPERO; ref CRD42017078778).

Search methods for identification of studies

MEDLINE/PubMed, Embase, Wiley Online Library, Cochrane Library and Web of Science databases were searched to identify trials of antacid therapy in preterm infants. Databases were screened for publications from the earliest available date until October 15, 2017. No language restrictions were applied. Ethical approval was not required because only published articles were included in this review. A database search of clinicaltrials.gov for ongoing and completed trials was also carried out, using the search terms infant or preterm and reflux or gastroesophageal reflux. Trials reported as abstracts or letters to the editor were included if sufficient data to fulfil the inclusion criteria was presented within the report, or provided by authors. Full search strategy is presented in supplementary Appendix 1.

Eligibility criteria

All relevant randomised trials involving preterm infants (<37 weeks gestation) with GORD (clinical diagnosis and/or 24-hour intraoesophageal PH monitoring, or impedance studies) receiving care on a neonatal unit. Crossover, randomised trials or Quasi-randomised studies,

described in some way as to suggest or imply that the study was randomised if the demographic detail of each group was similar were included.

Types of interventions

We included all available randomised controlled trials evaluating antacid therapies for gastro-oesophageal reflux in preterm neonates. Antacid therapy (administered by any method) should have been commenced after the diagnosis of GORD and continued for any duration.

The interventions considered were:

- H2 receptor antagonists versus a placebo or standard care/ non-pharmacological therapy.
- Proton pump inhibitors versus a placebo or standard care/ non-pharmacological therapy.
- Alginates versus a placebo or standard care/ non-pharmacological therapy.

Trials were not limited by dose, frequency or duration of intervention.

Selection of studies

Paired reviewers (ED, CM, BS, JD) independently screened titles, abstracts and then full texts for eligibility, assessed risk of bias, and collected data from included studies. Any disagreement between reviewers was resolved through discussion or adjudication by a third reviewer (BS, JD). In case of duplicate publications, the most recent and updated report of the study was included.

Risk of bias and quality of evidence assessment

The Cochrane Risk-of-Bias Tool was used to assess the risk of bias. [7] The quality of the evidence of outcomes was rated by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8]

Data extraction

From each eligible study the following information was collected: study characteristics (e.g., author name, year of publication, sample size, patient characteristics, antacid type, duration of intervention, dosage, and any of our pre-planned clinical outcomes.

Primary outcomes

A reduction in reflux symptoms assessed by a reflux index score or bedside symptom charts.[9] Clinical symptoms include the following: total GOR episodes, vomit/regurgitations, choking/coughing, bradycardia attributed to GOR, behavioural/crying, feeding difficulties, irritability or pain, recurrent postprandial apnoeas and oxygen desaturation within two hours postprandial period.

Secondary outcomes

- Time taken to establish full enteral feeds
- Length of hospital stay
- Necrotising enterocolitis (Bell's stage 2 or greater)
- Suspected or proven sepsis
- Other adverse effects

Statistical analysis

We planned to analyse treatment effects in the individual trials using Review Manager 5.3 software, with risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). However, given the small number of included studies, their varying methodologies and interventions we judged quantitative meta-analysis to be inappropriate and instead report a narrative description of each study. Data are presented as reported in individual studies. We had also planned to conduct

a number of subgroup analyses, which are detailed in the study protocol. The small number of studies, with small sample sizes and variable methods precluded subgroup analyses.

Results

Description of Studies

A total of 20139 records were identified by the initial search. 18909 were excluded as they were duplicates, or systematic reviews. 1230 titles and abstracts were screened and 1202 were excluded. 28 full text articles were assessed for eligibility and 6 studies met our inclusion criteria. (Figure 1)

All included studies were double-blind, randomised, placebo-controlled trials. 4 of the 6 were cross-over trials (Wheatley et al[10], Omari et al[11], Corvaglia (a) et al[12], Corvaglia (b) et al[13]), whilst the remaining 2 were parallel trials (Orenstein et al[14], Davidson et al[15]).

The main characteristics of included RCTs are described in Table 1 and excluded studies are summarized in supplementary appendix 2.

Table 1 - Characteristics of Included Studies

Studies	Corvaglia (a) et al[12]	Corvaglia (b) et al[13]	Davidson et al[15]	Omari et al[11]	Orenstein et al[14]	Wheatley et al[10]
Methods	Clinical trial - cross-over of treatment and placebo	Clinical trial - cross-over of treatment and placebo	Randomised, double blind, placebo controlled trial	Randomised, double-blind, placebo-controlled, crossover design trial	Multicentre, double-blind, randomised, placebo-controlled Trial	Randomised, controlled, blind cross-over study of treatment and placebo
Participants	32 Preterm newborns (gestational age ≤33 weeks)	28 Preterm newborns (gestational age ≤33 weeks)	52 Term infants or with a gestational or post-conceptional age of 28 to 44 weeks	10 Preterm infants with a mean postmenstrual age of 36.1 ± 0.7 (range, 34-40 weeks)	162 Infants aged 16 weeks (median, range 4-51) gestation at birth 35 weeks (median, range 25-39)	18 Preterm <37 weeks and corrected gestational age at enrolment <44 weeks
Diagnostic symptoms	Frequent regurgitations and/or postprandial desaturations)	Recurrent postprandial apnoeas	2 of the following clinical findings: apnoea +/- bradycardia; +/- oxygen desaturations, vomiting or gagging, and irritability or pain at least every second feed or at least twice every 8 hours	Infants with symptoms of GORD, confirmed by 24h pH monitoring with significant reflux index	Infants with symptomatic GORD who remained symptomatic within 1 hour after feeding despite at least 1 week of nonpharmacological management	Clinical diagnosis of GOR and bradycardia attributed to GOR by clinicians
Interventions	0.25 ml/kg sodium alginate was given four times at alternate meals (DG) meals), remaining	0.25 ml/kg sodium alginate after one single meal (DG meal) or placebo (DF meal)	Esomeprazole 0.5 mg/kg or placebo once daily for up to 14 days	Omeprazole (0.7mg/kg)or placebo (days 1–7) and then the alternative treatment regimen was	Lansoprazole administered once daily at 0.2 to 0.3 mg/kg/day for infants age ≤10 weeks and at 1.0 to 1.5 mg/kg/day for those	Metoclopramide (0.2 mg/kg/dose every 6 hours) and ranitidine (2 mg/kg/dose) every 8 hours or placebo. Each infant was

	four meals were placebo (DF meals)			given for the second week (days 8–14)	age >10 weeks or placebo (maximum 4 weeks of study drug treatment)	randomly assigned to 1 of 2 study groups
Primary Outcomes	Gastro-oesophageal reflux features (i.e. number, acidity, duration and height of GORs)	Apnoea episodes and Gastroesophageal features	Change from baseline to end of treatment in the total number of GORD-related symptoms and signs (vomiting, apnoea, bradycardia,oxygen desaturation, gagging, back arching, irritability, crying and fussing).	Gastric acidity, oesophageal acid exposure and the number and duration of acid reflux episodes	Number and duration of crying episodes during or ≤1 hour after feeding and frequency of various GORD symptoms quantified in daily diaries	Bradycardia episodes per day
Secondary Outcomes	NS	NS	Adverse Events	Number of vomiting, apnoea, bradycardia or behavioural changes	Adverse Events	NS

GORD: Gastro-Oesophageal Reflux disease; GOR: Gastro-Oesophageal Reflux; DG: drug-given; DF: drug- free; NS: not specified

Risks of Bias assessments of trials are summarized in Figure 2 and supplementary Appendix 3. The evaluations of the level of evidence of outcomes according to the GRADE approach are summarized in supplementary Appendix 4.

A total of 302 participants were enrolled in the 6 included trials, of which, 4 studies included only preterm infants. Omari et al[11] included preterm infants between 34 and 40 weeks gestational age, Corvaglia (a) et al[12] and Corvaglia (b) et al[13] included ≤33 weeks gestational age and Wheatley et al [10] included those with a gestational age of <37 weeks at birth and a corrected gestational age at enrolment of <44 weeks. Orenstein et al[14] and Davidson et al[15] included both

preterm infants and full-term infants. The inclusion criteria for each study defined GORD differently. (Table 1)

Primary Outcome: All 6 studies assessed various reflux symptoms. Four trials reported GOR episodes based on 24-hour pH/impedance monitoring. [11, 12, 13, 15] Three trials reported bradycardia (Davidson et al[15], Omari et al[11], Wheatley et al[10]) and three trials reported apnoea (Corvaglia (b) et al[13], Davidson et al[15], Omari et al[11]). The other reported outcomes included vomiting, apnoea, bradycardia, oxygen desaturation, gagging, back arching, and irritability/crying/fussing.[10, 11, 14, 15] None of the studies reported on the prespecified secondary outcomes, namely: time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis and suspected or proven sepsis. Orenstein et al looked at treatment-emergent adverse events and serious adverse events including upper respiratory tract infections, constipation, dermatitis, ear infections, fever, lower respiratory tract infection, respiratory tract congestion, rhinorrhoea, candidiasis, diarrhoea (excluding infective), vomiting, alkaline phosphatase increase, and others.

Effects of Interventions

Sodium Alginate (Gaviscon) vs Placebo

32 patients with a median gestational age of 30 weeks were enrolled in Corvaglia (a) et al.[12] Participants were fed 8 times over a 24 hour period, with meals alternatively given with drug ('drug-given' - DG) and without drug ('drug-free' - DF). 28 patients with a median gestational age of 30 weeks were enrolled in Corvaglia (b) et al.[13] Participants were studied between the hours of 9am and 6pm, when they were recorded twice, for 3 hours each time, after one DG meal and one DF meal, the order of which was randomly chosen.

There was significant decrease in total GOR episodes detected only by pH monitoring (pH-GORs), acid GOR episodes detected by multichannel intraluminal impedance monitoring (aMII-GOR), reflux index detected only by pH monitoring (RIpH) and Proximal GORs. [12,13]

All other outcomes were not significant (Liquid GORs, Mixed GORs, non-acid GOR episodes detected by multichannel intraluminal impedance monitoring (NaMII-GOR), non-acid MII-GOR-bolus exposure index (NaMII-GOR-BEI), and Distal GORs).[12] No differences in the number of total apnoea episodes, central apnoeas, obstructive apnoeas, mixed apnoeas, desaturations, bradycardia, pathological apnoeas were found between DG and DF periods (p value was not significant).[13](Table 2)

Table 2. Effect of Alginates (Gaviscon) use in preterm infants

Studies	Antacids	Control	p-value*
Corvaglia (a) et al [12]			
Total GORs	49.00 (28.50–67.00)	58.50 (33.50–75.75)	0.024
Liquid GORs	21.50 (12.25–32.00)	21.50 (13.50–39.75)	0.432
Gaseous GORs	2.00 (0.25–7.50)	3.00 (0.00–14.75)	0.040
Mixed GORs	3.00 (2.00–5.75)	3.00 (1.00–5.00)	0.614
pH-GORs	17.00 (6.00–29.75	29.00 (13.50–44.50)	0.002
aMII-GORs	4.00 (2.00–8.25)	6.00 (2.25–11.75)	0.050
NaMII-GORs	19.00 (10.00–32.75)	18.50 (8.50–33.75)	0.743
RIpH	4.0 (1.8–13.1)	7.6 (3.3–17.0)	0.030
aMII-GOR-BEI	0.2 (0.1–0.6)	0.4 (0.1–1.0)	0.036
NaMII-GOR-BEI	1.2 (0.5–1.9)	0.9 (0.5–1.7)	0.822
Distal GORs (no.)	18.00 (11.25–27.00	15.00 (9.25–26.00)	0.959
Proximal GORs (no.)	5.50 (4.00–9.00)	7.50 (3.00–12.00)	0.030
Corvaglia (b) et al [13]			
Total GOR episodes	9 (0–33)	20.5 (1–42)	0.001
pH-GOR	2 (0–26)	7.5 (0–23)	0.004
a-MII-GOR	1 (0–5)	3 (0–16)	0.001
Na-MII-GOR	4.5 (0–22)	6 (1–21)	0.145

RIpH	0.9 (0–23.2)	8.4 (0–44.2)	0.001
a-MII-BEI	0.17 (0–2)	0.5 (0–8.1)	0.002
Na-MII-BEI	0.75 (0–5.7)	1.0 (0.1-9.2)	0.982
Total apnoea episodes	9.5 (0–35)	9.5 (0–44)	0.99
Central apnoeas	3.5 (0–25)	5 (0–34)	0.22
Obstructive apnoeas	1 (0–8)	1 (0–10)	0.10
Mixed apnoeas	3 (0–16)	4 (0–17)	0.98
Desaturations	0.5 (0–10)	0 (0–12)	0.41
Bradycardia	0 (0–3)	0 (0–3)	0.32
Pathological apnoeas	0 (0–5)	0 (0–7)	0.69

GOR: Gastro-Oesophageal Reflux;MII: multichannel intraluminal impedance monitoring; pH-GOR: GOR episodes detected only by pH monitoring; aMII-GOR: acid GOR episode detected by MII; NaMII-GOR: non-acid GOR episode detected by MII; RIpH: Reflux Index detected only by pH monitoring; aMII-GOR-BEI: acid MII-GOR-bolus exposure index; NaMII-GOR-BEI: non-acid MII-GOR-bolus exposure index
Values are reported as median (interquartile range).
*p-values as provided in the original publication. The level of significance was set at $p \leq 0.05$.

Esomeprazole vs Placebo

52 patients with a mean gestational age of 31 were enrolled in the Davidson et al study. 1 did not have valid efficacy data and was excluded from the reported results. Participants were randomly selected to receive either esomeprazole (n=25) or placebo (n=26), once daily, for up to 14 days.[15] No significant results were obtained from this study, which was discontinued prematurely due to poor enrolment. [15](Table 3)

Table 3. Effect of Proton Pump Inhibitors use in preterm infants

Studies	**Antacids**	**Control**	**p-value***
Esomeprazole vs Placebo	**25 infants**	**26 infants**	
Davidson et al [15]			
Total number of GORD-related signs and symptoms, percentage of change from baseline after 14 days of treatment	-14.7%	14.1%	0.92
Gastrointestinal events, percentage of change from baseline	-8.39%	10.16%	0.42
Neurobehavioral events, percentage of change from baseline	-3.54%	-3.98%	0.94

Cardiorespiratory events, percentage of change from baseline	-38.94%	-41.17%	0.89
Omeprazole vs Placebo	**10 infants**	**10 infants**	
Omari et al [11]			
Gastric acidity (%time pH<4), mean±SEM	13.9 ± 5.1	53.8 ± 6.8	<0.0005
Oesophageal acid exposure (%time pH<4), mean±SEM	4.9 ± 3.4	19.0 ± 4.5	<0.01
No. of acid GOR episodes, mean±SEM	119.4 ± 20.	59.6 ± 26.7	<0.05
No. of oesophageal acid GOR >5min, mean±SEM	8.0 ± 2.1	3.0 ± 2.0	<0.01
Lansoprazole vs Placebo	**81 infants**	**81 infants**	
Orenstein et al [14]			
Primary efficacy: Responder rate, n (%)	44 (54%)	44 (54%)	NS
AEs, n (%)	50 (62%)	37 (46%)	NS
SAEs, n (%)	10 (12%)	2 (2%)	0 .032

GORD: Gastro-Oesophageal Reflux disease; GOR: Gastro-Oesophageal Reflux; SEM: standard error of mean; NS: not significant; AEs: adverse events; SAEs: serious adverse events.
*p-values as provided in the original publication.

Omeprazole vs Placebo

10 preterm infants with a mean postmenstrual age of 36.1 ± 0.7 weeks and mean postnatal age of 50 ± 9 days were enrolled in Omari et al.[11] Participants were given omeprazole for 7 days and placebo for 7 days in randomised order. At the end of each week of interventions, a 24-hr oesophageal and gastric pH monitoring study was performed. Analyses on the basis of pH recordings showed that Omeprazole therapy significantly reduced the oesophageal acid exposure % time pH<4 and reduced gastric acidity % time pH<4. [11] (Table 3). There were no significant changes to symptom frequency (vomiting, apnoea, bradycardia, choking, behavioural changes) or blood results.

Lansoprazole vs Placebo

162 patients were enrolled in Orenstein et al, 44 of whom were premature infants, with a median gestational age at birth of 35 (interquartile range 25-39) weeks.[13] Participants were randomly selected to take either lansoprazole (n=81) or a placebo (n=81) for up to 4 weeks. There was a

35% loss of follow up for participants receiving lansoprazole and 36% for participants receiving placebo. Lansoprazole and placebo produced identical responder numbers (54%). Responder status was defined as a ≥50% reduction from baseline in either percentage of feedings with crying episode(s) or duration (in minutes) of episodes averaged across feedings. No significant results were obtained from this trial. Serious adverse events (SAEs), particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo group (10 vs 2; P= 0.032). (Table 3)

Metoclopramide and Ranitidine vs Placebo

18 patients were enrolled, and 17 completed the study, with a gestational age of 29 ± 3 weeks. There was a significant decrease in the number of bradycardia episodes per day in the mean combined placebo time periods compared to the mean combined drug time periods [3.6 (SD 2.7) vs 4.6 (SD 3.1)), P = 0.04], and in bradycardia episodes over time (P<0.001), with fewer episodes during placebo periods. [10]

Discussion

This systematic review reveals that there is insufficient evidence to support the efficacy and safety of antacid therapies in preterm infants. 4 out of the 6 studies included in the review were cross over trials, where the patient receives both interventions at different time intervals. The carry-over effect, where the intervention taken in the first period is still effective when the second intervention is being taken, is a major limitation in crossover designs. These effects cannot be estimated separately. So as to minimise the risk of a carry-over effect, it can be effective allow a 'wash-out' period between interventions. Wheatley et al allowed a 24-hour washout period at the beginning of the second and third time periods.[10] Omari et al, Corvaglia (a) and Corvaglia (b) et al did not appear to have a wash-out period. [11, 12, 13] When deciding whether to use a cross over design, it is important to consider whether the outcome that is being treated

will change naturally over time. This does not seem like it would be an issue in the Corvaglia (a) and Corvaglia (b) studies, due to the overall treatment and observation period being short at just 24 hours. It may be problematic, however, for the Omari et al study, with each infant receiving a week of each intervention. Wheatley et al studied infants over a 2 week period and splits one intervention so it is given at the start and end of the 2 week period. This study shows a significant decrease in bradycardias over time, which may be evidential of a natural improvement of the outcome overtime, due to the infants' growth.[10]

Alginates

Sodium alginate significantly reduced acid GOR episodes, though had no effect on the reduction of apnoeas. Corvaglia (a) et al reports that participants were observed over a 24-hour period, and data was collected after 8 meals. There may have been selective reporting in the Corvaglia (b) et al study, with authors only reporting data from a 6-hour period of observation instead of the full 24-hour data, thus presenting more significant results. This discrepancy diminishes the validity of the reports and applicability to clinical practice.

Proton pump inhibitors

Omari et al showed that 0.7 mg/kg omeprazole given once daily was effective in reducing the frequency of acid reflux episodes and the overall degree of oesophageal acid exposure in premature infants.[11] Despite the normalization of acid reflux in most patients, the number of symptomatic events was not significantly changed. The drug-dosing regimen used appeared safe based on adverse event (AE) reporting and blood screening. However, due to the small number of participants enrolled in the study (n=10), it would be difficult to state whether this evidence is applicable in everyday practice and more trials must be carried out into the efficacy of omeprazole. There were no significant differences in the number of GORD-related signs and symptoms between neonates receiving esomeprazole or lansoprazole vs placebo.[14, 15] SAEs occurred more frequently with lansoprazole than with placebo group. It is unclear whether loss to follow up caused a significant imbalance in characteristics between lansoprazole and placebo

group. Therefore, applicability into everyday practice is low because loss to follow-up can severely compromise validity as those lost to follow-up could have a different prognosis than those who complete the study. The number of AEs was similar between neonates receiving esomeprazole vs placebo. Both Orenstein et al and Davidson et al had notable conflicts of interest that were reported in the study, as shown in the Table of Bias. (Appendix 3) The trials of both studies were sponsored by drug companies, which may have affected the design and outcomes of the trial as well as the reporting of results. However, no significant results were found in either trial, and so no results were reported in favour of the drug under trial.[14, 15]

H2-receptor antagonists

A retrospective cohort study conducted by Romainea et al. [16] in USA concluded that H2 blocker use was associated with increased risk of the combined outcome of death, NEC, or sepsis in hospitalized VLBW infants. Another recent retrospective cohort study showed that ranitidine use was associated with an increased risk of infections and mortality in preterm infants, but not with NEC.[17] Wheatley et al showed that ranitidine did not reduce, and may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GOR.[10] Wheatley compared the combination of 2 interventions together against a placebo, ranitidine, a H2 receptor antagonist and metoclopramide, a dopamine receptor antagonist. With regards to applicability, the data derived from this study actually suggests that combining ranitidine and metoclopramide may be detrimental to patients and should therefore be avoided in clinical practice, as it showed a significant increase in bradycardia episodes during drug periods. This may be caused by significant interactions between the 2 drugs that could either decrease the efficacy of either or both of drugs or perhaps cause adverse effects. Leucuta et al, found pharmacokinetic changes, such as an increased half-life, in metoclopramide, when taken with ranitidine.[18] It is also quite likely that this is a chance finding, given the small number of participants enrolled in the study (n=18). Previous studies into the combined efficacy of ranitidine and metoclopramide suggest

that this treatment is effective at increasing gastric pH and reducing the side effects of GORD, and do not mention any significant drug induced side effects or drug interactions.[19,20]

Limitations

A number of limitations are worth noting, not all studies met the inclusion criteria outlined in the methods. We initially stated that only preterm infants <37 weeks gestation were to be included in this review, however both Davidson et al and Orenstein et al included data for full-term infants as well as preterm, some of whom were >37 weeks gestation. Authors were contacted to obtain exclusively preterm data, however, replies were not received. We included these studies in this review due to the high percentage of preterm infants enrolled in the trials. The methods stated that the only interventions that were to be considered were H2 receptor antagonists, proton pump inhibitors and alginates, however Wheatley et al assessed the combined effects of both metoclopramide (dopamine receptor antagonist) and ranitidine (H2 receptor antagonist).[10] We still decided to report this outcome as the inclusion of the H2 receptor antagonist as it is of interest to the reader in general who must bear in mind this was a combined intervention. Studies included in the review were heterogeneous in terms of design, study characteristics such as age of participants and interventions considered for the treatment of GORD. Studies also had small sample sizes. This limits the conclusions that can be drawn from this review however it highlights the gaps in the evidence.

Agreements or disagreements with other studies or reviews

To our knowledge, this review is the first to look into the effects of antacids in preterm infants. Terrin et al. in a retrospective study of 274 very low birth weight infants reported that the risk of necrotizing enterocolitis, nosocomial infection and mortality were significantly higher in the infants exposed to ranitidine.[4] However, non-prospective, non-controlled and un-blinded design features limited its significance. A Cochrane review by Tighe et al looking at the effects of

pharmacological treatment for the management of GORD in children concluded that although there is evidence to support pharmacological use in older children, use in infants is unsupported due to lack of robust RCT evidence.[21]

Cohen et al. in a recent review suggested that the use of GORD medications should only be used after non-pharmacological measures have been taken with incomplete success as acid suppression may place immune-deficient infants and children at risk for the development of lower respiratory tract infections and nosocomial sepsis. [22]

Author's Conclusions

There is insufficient evidence on the efficacy and safety of antacids in preterm infants.

The lack of research in this area of medicine is a problem that must be addressed in this population of patients. Adequately powered, randomised, controlled trials in preterm infants are needed to determine the safety and efficacy of these commonly used medications.

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Study concept and design: Dr. Dorling and Dr. Schoonakker conceived and designed the study.

Acquisition of data: Dr. Mackie and Dr. Dermyshi.

Analysis and interpretation of data: Dr. Dermyshi, Dr. Mackie, Dr. Kigozi, Dr Schoonakker and Dr. Dorling.

Drafting of the manuscript: Dr. Dermyshi, Dr. Kigozi, Dr. Dorling.

Critical revision of the manuscript for important intellectual content: Dr. Dorling

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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References

1. Corvaglia L, Monari C, Martini S, et al. Pharmacological therapy of gastroesophageal reflux in preterm infants. *Gastroenterol Res Pract*. 2013; 2013:714564. doi: 10.1155/2013/714564.

2. Rossor T, Andradi G, Bhat R Greenough A. Investigations and management of gastro-oesophageal reflux in United Kingdom neonatal intensive care units Acta Paediatrica 2018 January; DOI:10.1111/apa.14073.

3. Guillet R, Stoll BJ, Cotten CM, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; 117(2):e137-42.

4. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012 Jan;129(1):e40-5. doi: 10.1542/peds.2011-0796.

5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009 Oct; 62(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006.

6. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (updated March 2011). *The Cochrane Collaboration* 2011 (Available at: www.cochrane-handbook.org.).

7. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011 Oct 18; 343:d5928. doi: 10.1136/bmj.d5928.

8. Guyatt G, Oxman AD, Akl EA, et al: GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011 Apr; 64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026.

9. Orenstein SR, Cohn JF, Shalaby TM, et al. Reliability and validity of an infant gastroesophageal reflux questionnaire. Clin Pediatr(Phila)1993; 32:472–484.

10. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr*. 2009 Oct; 155(4):516-21. doi: 10.1016/j.jpeds.2009.03.044.

11. Omari TI, Haslam RR, Lundborg P, et al. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. *Journal of pediatric gastroenterology and nutrition* 2007; 44(1):41-4.

12. (a) Corvaglia L, Aceti A, Mariani E, et al. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants. *Aliment Pharmacol Ther.* 2011 Feb; 33(4):466-70. doi: 10.1111/j.1365-2036.2010.04545.x.

13. (b) Corvaglia L, Spizzichino M, Zama D, et al. Sodium Alginate (Gaviscon(R)) does not reduce apnoeas related to gastro-oesophageal reflux in preterm infants. *Early Hum Dev.* 2011 Dec; 87(12):775-8. doi: 10.1016/j.earlhumdev.2011.05.013.

14. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr.* 2009 Apr; 154(4):514-520.e4. doi: 10.1016/j.jpeds.2008.09.054.

15. Davidson G, Wenzl TG, Thomson M, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *J Pediatr*. 2013 Sep; 163(3):692-8.e1-2. doi: 10.1016/j.jpeds.2013.05.007.

16. Romainea A, Ye D, Ao Z, et al. Safety of Histamine-2 Receptor Blockers in Hospitalized VLBW Infants. *Early Hum Dev.* 2016 Aug; 99:27-30. doi: 10.1016/j.earlhumdev.2016.05.010.

17. Santana RNS, Santos VS, Ribeiro-Júnior RF, et al. Use of ranitidine is associated with infections in newborns hospitalized in a neonatal intensive care unit: a cohort study. *BMC Infect Dis.* 2017 May 30; 17(1):375. doi: 10.1186/s12879-017-2482-x.

18. Leucuţa A, Vlase L, Farcău D, et al. Pharmacokinetic interaction study between ranitidine and metoclopramide. *Romanian journal of gastroenterology* 2004; 13(3):211-4.

19. Hong J-Y. Effects of Metoclopramide and Ranitidine on Preoperative Gastric Contents in Day-Case Surgery. *Yonsei Medical Journal* 2006; 47(3):315-318. doi:10.3349/ymj.2006.47.3.315.

20. Bala I, Prasad K, Bhukal I, et al. Effect of preoperative oral erythromycin, erythromycin-ranitidine, and ranitidine-metoclopramide on gastric fluid pH and volume. *J Clin Anesth.* 2008 Feb; 20(1):30-4. doi: 10.1016/j.jclinane.2007.08.002.

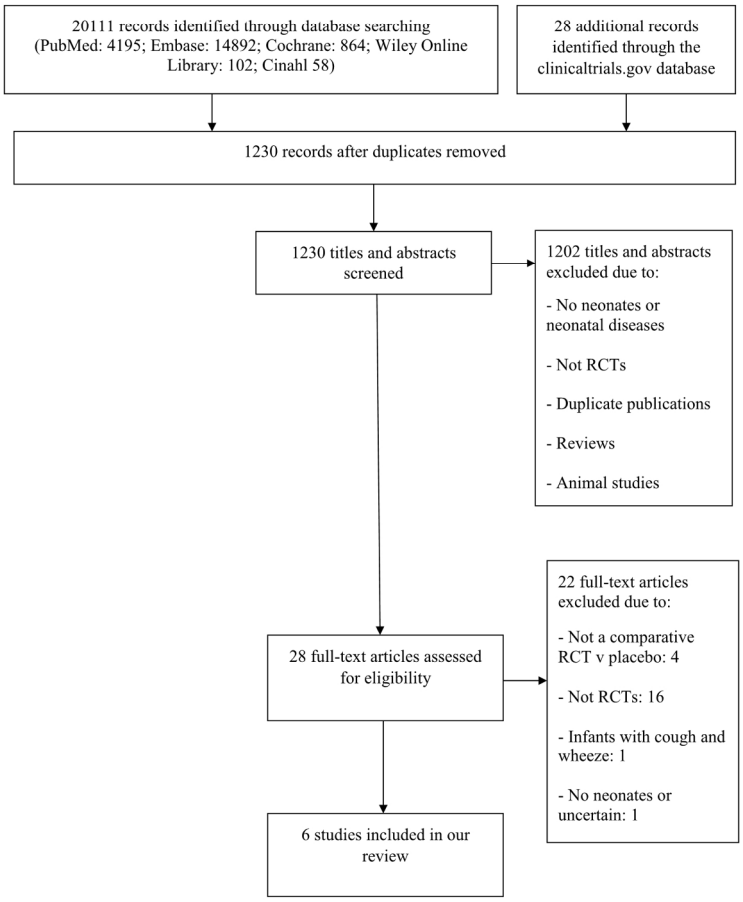
21. Tighe M, Afzal NA, Bevan A, et al. Pharmacological treatment of children with gastrooesophageal reflux (Review). *Cochrane Database Syst Rev*. 2014 Nov 24; (11):CD008550. doi: 10.1002/14651858.CD008550.pub2.

22. Cohen S, Bueno de Mesquita M, et al. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. *Br J Clin Pharmacol.* 2015 Aug; 80(2):200-8. doi: 10.1111/bcp.12619.

Tables

Figures

Figure 1: Study flow diagram



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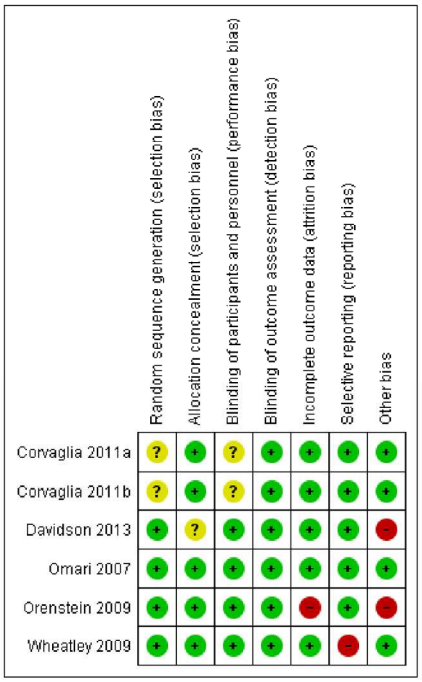

Figure 2- Risk of Bias Summary

583x825mm (72 x 72 DPI)

Appendix 1 Search strategies

Search Methods for Identification of Studies

The standard search of the Cochrane Neonatal Review Group, including electronic searches of the Cochrane central register of controlled trials (CENTRAL, The Cochrane Library), MEDLINE (1966 – to present), EMBASE (1980- to present) and CINAHL (1982 –to present) was used. There was no language restriction applied.
The following search terms were applied for each database:

MEDLINE (via PubMed) was searched using the following search strategy:

#1	(infant) OR infants	(infant) OR infants
#2	(neonate) OR neonates	(neonate) OR neonates
#3	(preterm) OR preterms	(preterm) OR preterms
#4	(preterm) AND (neonate OR neonates OR infants)	(preterm) AND (neonate OR neonates OR infants)
#5	(gastroesophageal reflux) AND infants	(gastroesophageal reflux) AND infants
#6	(gastroesophageal) AND reflux	(gastroesophageal) AND reflux
#7	(((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants))	(#6) AND (#4)
#8	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) NOT animals	(#7 NOT animals
#9	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND (therapy OR therapeutic OR therapeutics)	(#7) AND (therapy OR therapeutic OR therapeutics)
#10	(((((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND (therapy OR therapeutic OR therapeutics))) NOT animals	(#9 NOT animals
#11	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND alginates	(#7) AND alginates
#12	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND rabeprazole	(#7) AND rabeprazole
#13	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND pantoprazole	(#7) AND pantoprazole

#14	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND omeprazole	(#7) AND omeprazole
#15	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND proton pump inhibitors	(#7) AND proton pump inhibitors
#16	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND esomeprazole	(#7) AND esomeprazole
#17	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND ranitidine	(#7) AND ranitidine
#18	((((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND histamine h2 receptors) AND antagonist	(#7) AND (histamine h2 receptors) AND antagonist
#19	((((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND histamine h2 receptors) AND antagonist Schema: all	(#7) AND (histamine h2 receptors) AND antagonist) Schema: all
#20	(Controlled clinical trial[tw] OR Clinical Trial[tw] OR Clinical trial [ptyp] OR Controlled)	(Controlled clinical trial OR Clinical Trial OR Clinical trial OR Controlled)
#21	(Randomized Controlled Trial[tw] OR Randomized Controlled Trial[ptyp] OR random* [tw])	(Randomized Controlled Trial OR Randomized Controlled Trial OR random)
#22	(((((gastroesophageal) AND reflux)) AND ((preterm) AND (neonate OR neonates OR infants)))) AND ((Randomized Controlled Trial[tw] OR Randomized Controlled Trial[ptyp] OR random* [tw]))	(#7) AND (#21)

EMBASE was searched using the following search strategy:

1.	prematurity/ or preterm.mp.
2.	newborn/
3.	infant/
4.	gastroesophageal reflux.mp. or gastroesophageal reflux/

5.	reflux.mp.
6.	antacid.mp. or antacid agent/
7.	clinical trial/
8.	proton pump inhibitors.mp. or proton pump inhibitor/
9.	histamine H2 receptor antagonist/
10.	alginate.mp. or alginic acid/
11.	1 and 4
12.	6 and 11
13.	1 and 6
14.	7 and 11
15.	8 and 11
16.	9 and 11
17.	10 and 11
18.	12 or 14 or 15 or 16 or 17
19.	7 and 18
20.	random.mp.
21.	19 and 20

COCHRANE Library (CENTRAL and Cochrane Database of Systematic Reviews) were searched using the following search strategy:

#1	preterm
#2	prematurity
#3	neonate or neonates

#4	newborn
#5	infant or infants
#6	gastroesophageal reflux
#7	reflux
#8	antacid
#9	proton pump inhibitors
#10	H2 antagonist
#11	alginate
#12	clinical trials
#13	randomised
#14	#1 or #2 or #3 or #4 or #5 and #6
#15	#14 and #8
#16	#15 and #12
#17	#16 and #13

Cinahl: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial) AND (gastroesophageal reflux OR reflux) AND antacid)

Appendix 2

Characteristics of Excluded Studies

Excluded Study	Reason for Exclusion
Abdel-Rahman 2004	Not a RCT; uses different doses of Nizatidine
Adamko 2012	Exclude as infants with cough and wheeze.
Atasay 2010	Not a RCT.
Cresi 2006	Not a RCT
Dhillon 2004	Not a RCT
Golski 2010	Not a RCT
Kierkus 2011	Not a RCT, compared 2 different doses of Pantoprazole
Le 1992	Not a RCT, compared 2 different doses of Alginate
Loots 2014	States that patients have been 'referred' so assumed that these are GP patients and not preterm infants.
Omari 2009	Not a RCT.
Orenstein 2005	Comparison of 2 doses of Nizatidine
Sandstrom 2012	Not a comparative RCT v placebo (different doses of esomeprazole)
Springer 2008	Not a RCT.
Sutphen 1986	Not a RCT
Tammara 2011	Compared 2 doses of pantoprazole, did not use placebo.
Ward 2010	Compares 2 doses of pantoprazole
Weldon 1972	Not a RCT
Wenning 2005	Not a RCT
Zhang 2008	Not a RCT
Slaughter 2016	Not RCT
Santana 2017	Not RCT
Romaine 2016	Not RCT

Appendix 3

Risk of bias in included studies

When assessing the quality of RCTs, bias is a very important consideration. We have looked at the various areas where bias may arise throughout the trials and given this an overall level of risk.

Selection

Allocation was randomised with Davidson et al using block randomisation, and with Omari et al, Orenstein et al and Wheatley et al using a random number generator. Corvaglia (b) et al and Corvaglia (a) et al did not report any form of random sequence generation for allocation. With regards to allocation concealment, Davidson et al is unclear about its methods of concealment.

Performance

Davidson et al, Omari et al, Orenstein et al and Wheatley et al all state or imply that their placebo was prepared and appeared similar to the drug, thus ensuring the blinding of participants and personnel. Corvaglia (b) et al and Corvaglia (a) et al were not clear about their methods taken to ensure blinding.

Detection

Data were assessed by independent assessors for Corvaglia (b) et al, Corvaglia (a) et al, Davidson et al and Wheatley et al minimising risk of detection bias. No apparent detection bias was found in Omari et al and Orenstein et al.

Attrition

Corvaglia (a) et al, Corvaglia (b) et al and Omari et al reported all outcomes. Davidson et al and Wheatley et al both lost 1 participant each to follow-up during the study; Davidson et al was due to efficacy data not being available, Wheatley et al does not give an explanation. 57 of 162 participants in Orenstein et al discontinued the treatment early giving a high risk of attrition bias. 55 of these participants went on to take open-label lansoprazole, the results of which were reported and incomplete data was carried forward to the 4th week for the double-blind results. It is unclear what happened to the remaining 2 participants.

Risk of Bias Table – Corvaglia (b) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear Risk	The DG ('drug-given') meal was randomly chosen in order to avoid any possible carry-over effect. As same study as Corvaglia (a) et al, it seems this was a random choice of data from 2 DG ('drug-given') and DF ('drug-free') feed in a 9 hour window.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	The investigator was blind to the administration of sodium alginate. pH-MII and PSG data were analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

Risk of Bias Table - Corvaglia (a) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear Risk	Each patient assessed over 24 hour period; 8 feeds with 2nd, 4th, 6th and 8th feed was DG ('drug-given') meal. No randomisation used.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	During layout analysis the investigator was blind to the administration of sodium alginate. pH-MII and PSG data were then analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

Risk of Bias Table – Davidson et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A block randomisation scheme was used, stratified by centre.
Allocation concealment (selection bias)	Unclear Risk	Method of randomisation allocation not clearly described.
Blinding of participants and personnel (performance bias)	Low Risk	Treatments blind to all, method described but not explicit that the active and placebo preparations looked identical.
Blinding of outcome assessment (detection bias)	Low Risk	Two blinded central readers independently reviewed the videos and cardiorespiratory data.
Incomplete outcome data (attrition bias)	Low Risk	One patient in the placebo group completed the study, but was lost to follow-up between study completion and the safety follow-up visit.
Selective reporting (reporting bias)	Low Risk	One patient in the esomeprazole group was excluded from the modified ITT analysis because of invalid efficacy measurements.
Other bias	High Risk	Sponsored by AstraZeneca LP (Wilmington, Delaware). AstraZeneca was involved in the design and conduct of the study; collection, analysis, and interpretation of the data; and the preparation, review, and approval of the trial report manuscript. 2 authors, both funded by AstraZeneca developed the first draft of the trial report manuscript. 3 employees of AstraZeneca, included work on this manuscript among their job responsibilities and also had limited AstraZeneca stock ownership. 3 authors had received grants and research support from AstraZeneca.

Risk of Bias Table – Omari et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A stock solution containing either 5mg/mL omeprazole or sterile water was prepared and dispensed by pharmacy according to a randomisation schedule determined using a random number generator.
Allocation concealment (selection bias)	Low Risk	Drug or placebo prepared and dispensed using random number generator.
Blinding of participants and personnel (performance bias)	Low Risk	A stock solution was prepared which contained either omeprazole or sterile water (placebo). It is not clear how similar these were.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent detection possible.
Incomplete outcome data (attrition bias)	Low Risk	Follow up data complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	AstraZeneca R&D Molndal assisted by performing plasma omeprazole assays.

Risk of Bias Table – Orenstein et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Double-blind treatment assignments were made through a central web-based system according to a schedule that was computer generated.
Allocation concealment (selection bias)	Low Risk	States that treatment assignments were concealed to study personnel
Blinding of participants and personnel (performance bias)	Low Risk	Appearance, reconstitution, and administration of lansoprazole and placebo were identical.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent bias in outcome assessment.
Incomplete outcome data (attrition bias)	High Risk	55 of 162 discontinued treatment early for open label treatment. For such subjects, the last week of available data was carried forward to 4th week for the individual symptoms and global severity assessments.
Selective reporting (reporting bias)	Low Risk	All randomised infants administered 1 or more dose(s) of study drug were included in the intention-to-treat data set for efficacy and safety analyses.
Other bias	High Risk	Takeda Global Research & Development Center, Inc sponsored the clinical trial, employed 2 authors and data interpretation and analysis was also undertaken by their employees.

Risk of Bias Table – Wheatley et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Study group assignment (order of medication and placebo administration) was determined by blocked random number generation.
Allocation concealment (selection bias)	Low Risk	A research pharmacist assigned the study group for each patient at the time of enrolment.
Blinding of participants and personnel (performance bias)	Low Risk	Investigators, clinicians, and parents were all blind to the group assignment during the study period. Intravenous preparations were used because they were clear and colourless. Saline placebos of the same volume and colour were administered during the placebo periods.
Blinding of outcome assessment (detection bias)	Low Risk	At the end of the study period for each infant, after the study outcome data were summarised for the infant, the investigator contacted the pharmacist to ascertain the group assignment (order of medication and placebo administration) for the infant, eliminating bias as data were analysed prior to finding out group assignment.
Incomplete outcome data (attrition bias)	Low Risk	One infant was enrolled in the study but was then withdrawn, with no explanation for the withdrawal.
Selective reporting (reporting bias)	High Risk	Clinicaltrials.gov record shows that the authors originally planned to analyse and present data on apnoea also. This was not included and the protocol was changed on clinicaltrials.gov.
Other bias	Low Risk	No conflicts of interest or sponsorship.

Appendix 3

sTable 1- Summary of findings: Sodium alginate in preterm infants

Sodium alginate compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: Sodium alginate **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes assessed with: Combined pH and impedance monitoring (follow-up: range 6h to 24h)	In two studies Sodium alginate significantly decreased the number of acid GOR episodes but did not influence the number of non-acid GOR episodes. In one study Total GOR Episodes: RR 0.59 (0.53 to 0.65) (95% CI). In the other study, sodium alginate significantly decreased the number of GOR (DG vs. DF: median 49 vs. 58.5) [a,b,c]	60 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]
A reduction in reflux symptoms (apnoea related to GOR) assessed with: Combined multichannel intraluminal impedance and pH monitoring and polysomnography (follow-up: 6h)	The frequency of apnoeas related to GOR did not differ between DG and DF meals (median [range] 0 [0–0.67] vs. 0 [0–0.47]). Total Apnoea Episodes: RR 1.06 (0.96 to 1.18) (95% CI) [a,b]	28 (1 RCT)	⨁⨁◯◯ LOW [d,e]
Adverse events assessed with: Not specified (follow-up: range 6h to 24h)	No adverse event was recorded during the study period.	60 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	None of the included studies examined the effect of sodium alginates on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. DG: drug given

b. DF: drug free

c. GOR: gastroesophageal reflux

d. Evidence downgraded by 1 point (-1) for risk of selection bias.

e. Evidence downgraded by 1 point (-1) for indirectness as only a single study contributed data, and evidence was therefore based on a single patient population.

sTable 2 - Summary of findings: Proton pump inhibitors in preterm infants

Proton pump inhibitors compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: Proton pump inhibitors **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes assessed with: Twenty-four-hour esophageal pH monitoring (reflux index score)	Omeprazole therapy (10 participants; 1 study) significantly reduced gastric acidity, oesophageal acid exposure and the number and duration of acid reflux episodes compared to placebo. There was no statistically significant difference between the esomeprazole and placebo groups in the percentage of change from baseline after 14 days of treatment in the total number of GORD-related signs and symptoms (52 participants; 1 study).	62 (2 RCTs)	⊕⊕◯◯ LOW [a,b]
A reduction in reflux symptoms assessed with: Bedside symptom charts (vomit/regurgitations, choking/coughing, bradycardia attributed to GOR, behavioural/crying, feeding difficulties, irritability or pain, recurrent postprandial apnoeas and oxygen desaturation within two hours postprandial period)	Despite the normalization of acid reflux in most patients, the number of symptomatic events of vomiting, apnea, bradycardia or behavioral changes was not significantly changed by omeprazole (10 participants; 1 study). One study (162 participants) detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GORD. No significant differences were observed between the esomeprazole and placebo groups (52 participants; 1 study) in the percentage of change from baseline to the end of treatment in the total number of gastrointestinal, neurobehavioral or cardiorespiratory events.	224 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c]
Adverse events	Treatment-emergent serious AEs (SAEs), particularly lower respiratory tract infections, were significantly more frequent in the lansoprazole group compared with the placebo group (10 vs 2; P.032). Overall, few adverse events (AEs) were reported, and the number of patients with AEs was similar between the esomeprazole and placebo groups. The most commonly reported AE was decrease in oxygen saturation (52 participants; 1 study). No SAEs were reported in the esomeprazole-treated patients and 4 SAEs (neonatal bradycardia, cyanosis, inappropriate device signal detection, and infantile apneic attack) were reported in 3 placebo patients. Omeprazole therapy (10 participants; 1 study) was not associated with the occurrence of any serious adverse events.	224 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	None of the included studies examined the effect of proton pump inhibitors on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(0 studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

sTable 3 - Summary of findings: H2 receptor antagonists in preterm infants

H2 receptor antagonists compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: H2 receptor antagonists **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes	The included study did not examined the effect of H2 receptor antagonists on the reduction of reflux episodes.	(0 studies)	-
A reduction in reflux symptoms (Bradycardia) assessed with: Telemetry and nursing documentation	No evidence of efficacy was found for Ranitidine to reduce bradycardia. The mean number of bradycardia episodes per day in the combined drug periods was 4.6 (SD = 3.1), and the mean number of episodes per day in the combined placebo periods was 3.6 (SD = 2.7) There was a statistically significant difference, with fewer episodes during the placebo periods. The mean difference (drug minus placebo) was 0.94 episodes per day, with a P value of 0.04.	17 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Adverse events assessed with: Clinical assessment	There were no adverse effects attributed to ranitidine. However, it may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GOR.	17 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	No studies examined the effect of H2 receptor antagonists on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(0 studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect